IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 6,417,175

Inventors: Tomoyasu Ishikawa, Shohei Hashiguchi, Yuji Iizawa

Assignee: Takeda Pharmaceutical Company Limited

Title: PHOSPHONOCEPHEM DERIVATIVES, PROCESS FOR THE PREPARATION OF THE SAME, AND USE THEREOF

Issue Date: July 9, 2002

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Mail Stop: **Hatch-Waxman PTE**
Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

Sir:

Foley and Lardner LLP, acting under a general power of attorney for the patent owner Takeda Pharmaceutical Company Limited (Takeda) hereby requests an extension of the term of U.S. Patent No. 6,417,175 ("the '175 patent") pursuant to 35 U.S.C. § 156. A copy of the '175 patent is attached as Exhibit A. The assignment of the '175 patent from the inventors to Takeda Chemical Industries Limited has been recorded at Reel 010902, Frame 0251 on June 6, 2000. The change of name from Takeda Chemical Industries Limited to Takeda Pharmaceutical Company Limited (Takeda) has been recorded at Reel 015612, Frame 0101. A copy of the recorded assignment and change of name to Takeda is attached as Exhibit B. A Limited Power of Attorney that appoints the undersigned to act on behalf of Takeda before the U.S. Patent and Trademark Office for the purpose of filing this Request is attached as Exhibit C.

A total of three copies of this Request are submitted in compliance with 37 C.F.R. § 1.740(b) and as suggested by MPEP § 2753.

As permitted by 37 C.F.R. § 1.785(b) and MPEP § 2761, Foley and Lardner LLP is filing a request for patent term extension of U.S. Patent No. 6,906,055 based upon the same regulatory review period. Enclosed as Exhibit 1 is a copy of the Forest Laboratories, Inc. regulatory activity authorization letter in support of Application for Extension of Patent Term Under 35 USC §156.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740, and follows the numerical format set forth in 37 C.F.R. § 1.740(a):

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product will be marketed under the trademark TEFLARO™ in 400 mg, 600 mg vials for injection for the treatment of:

(1) Acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae, and Klebsiella oxytoca;* and

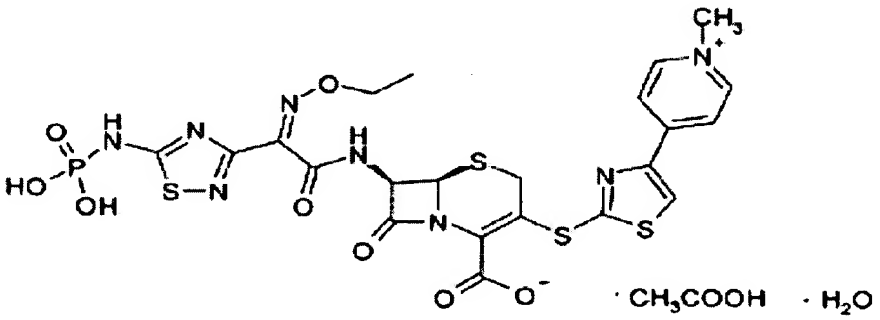
(2) Community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae, Klebsiella pneumoniae, Klebsiella oxytoca,* and *Escherichia coli.*

A copy of the approved package insert for TEFLARO™ is attached as Exhibit D. The active ingredient of TEFLARO™ has

(a) the chemical name (6*R*,7*R*)-7-{(2*Z*)-2-(ethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido}-3-{[4-(1-methylpyridin-1-ium-4-yl)-1,3-thiazol-2- yl]sulfanyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate monoacetate monohydrate;

(b) the generic name ceftaroline fosamil;

(c) the structural formula:



(d) the empirical formula $C_{22}H_{21}N_8O_8PS_4.C_2H_4O_2.H_2O$; and

(e) a molecular weight of 762.75.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The regulatory review occurred under Section 505(b) of the Federal Food, Drug and Cosmetic Act (FFDCA), which is codified at 21 U.S.C. § 355(b). Section 505(b) (21 U.S.C. § 355(b)) provides for the submission and approval of New Drug Applications (NDAs).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

TEFLARO™ received permission for commercial marketing from the Food and Drug Administration (FDA) pursuant to Section 505(b) of the FFDCA (21 U.S.C. § 355(b)) on October 29, 2010. A copy of the letter from the FDA approving marketing of TEFLARO™ is attached as Exhibit E.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in the approved product is ceftaroline fosamil. Ceftaroline fosamil was not previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act prior to the approval on October 29, 2010.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

TEFLARO™ was approved for commercial marketing on October 29, 2010. The sixty day period expires on Monday, December 27, 2010, assuming October 29 is the first day of the sixty day period. The present application, therefore, is timely filed within the sixty day period.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

Inventors: Tomoyasu ISHIKAWA, Shohei HASHIGUCHI, Yuji IIZAWA

Patent No.: 6,417,175

Issue Date: July 9, 2002

Expiration Date: December 17, 2018

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A copy of the '175 patent is attached as Exhibit A.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

No disclaimers or certificates of correction have been submitted or issued for the '175 patent.

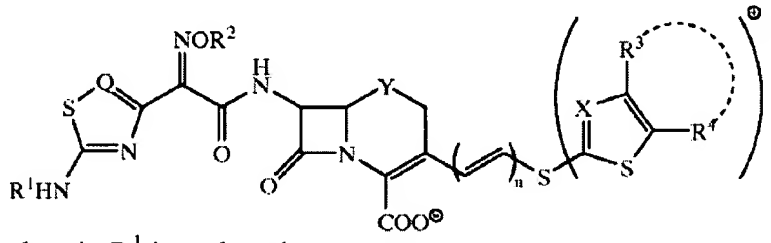
The 3½ and 7½ year maintenance fees for the '175 patent have been timely paid. A copy of the receipt showing payment of the 3½ and 7½ year fees is attached as Exhibit F.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

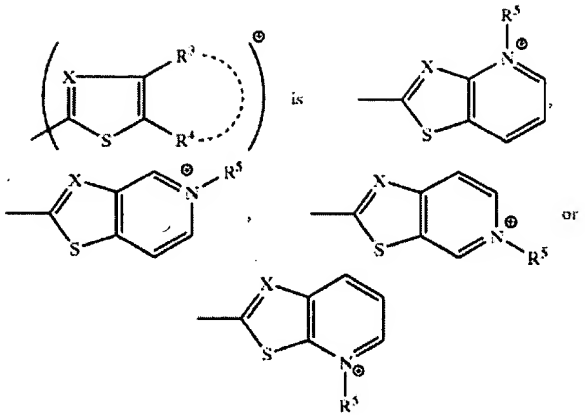
- **(i) The approved product, if the listed claims include any claim to the approved product;**
- **(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and**
- **(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.**

The '175 patent claims the approved product, ceftaroline fosamil; compositions of the approved product, methods for producing compositions of the approved product; and methods of using the approved product for treatment of bacterial infections. Each applicable patent claim is set forth below together with a showing of the manner in which each applicable patent claim reads on the approved product.

1. A compound of the formula:



wherein R^1 is a phosphono group;
R^2 is a hydrogen atom, an optionally substituted C_{1-6} alkyl group or a C_{3-5} cycloalkyl group;
each of Q and X is a nitrogen atom or CH;
Y is S;
n is 0 or 1;
one of R^3 and R^4 is a pyridinium group which may be substituted and the other is a hydrogen atom or a hydrocarbon group which may be substituted, or R^3 and R^4 taken together may form a quaternized nitrogen-containing heterocyclic ring which may be substituted, wherein when R^3 and R^4 are taken together, the group of the formula



wherein R^5 is an optionally substituted hydrocarbon group; or salt thereof.

Independent claim 1 is directed to a chemical genus encompassing the approved product, ceftaroline fosamil (where R^1 is a phosphono group; R^2 is ethyl (i.e., a C_{1-6} alkyl group); Y is S, Q is N, X is N, n is 0; and one of R^3 and R^4 is a pyridinium group while the other is hydrogen). See Exhibit D, Section 11.

> 2. 7β-[2(Z)-ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazole-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate.

Independent claim 2 is directed to the approved product (ceftaroline fosamil). See Exhibit D, Section 11.

> 3. A method for producing a pharmaceutical composition comprising mixing a compound of claim 1 with a pharmaceutically acceptable carrier, diluent or bulking agent.

Dependent claim 3 is directed to methods for producing compositions of a chemical genus encompassing the approved product (ceftaroline fosamil). See Exhibit D, Section 11.

> 4. 7β-[2(Z)-ethoxyimino-2-(5-phosphonoamino 1,2,4-thiadiazole-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolythio]-3-cephem-4-carboxylate or its salt.

Independent claim 4 is directed to the approved product (ceftaroline fosamil). See Exhibit D, Section 11.

> 5. A method for treating a bacterial infection which comprises administering an effective amount of a compound as claimed in claim 1 to a patient suffering from the bacterial infection.

Dependent claim 5 is directed to methods for using a chemical genus encompassing the approved product (ceftaroline fosamil) for the treatment of bacterial infections. The approved product is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae, and Klebsiella oxytoca.* The approved product is also indicated for the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae, Klebsiella pneumoniae, Klebsiella oxytoca,* and *Escherichia coli. See* Exhibit D; Section 1.

> 6. A method for treating a bacterial infection which comprises administering an effective amount of a compound as claimed in claim 1 together with at least one of pharmaceutically acceptable carriers, diluents and excipients to a patient suffering from the bacterial infection.

Dependent claim 6 is directed to methods for using a chemical genus encompassing the approved product (ceftaroline fosamil) for the treatment of bacterial infections. The methods include administering the claimed genus together with a carrier, diluent and/or excipient. The approved product is administered together with a carrier, diluent and/or excipient and is indicated for the treatment of specified bacterial infections. *See* Exhibit D; Sections 1-2 and 11.

7. A method as claimed in claim 5, wherein the bacterial infection is a MRSA infection.

Dependent claim 7 is directed to methods of using a chemical genus encompassing the approved product (ceftaroline fosamil) for treating methicillin-resistant *Staphylococcus aureus* (MRSA) infections. The approved product is indicated for the treatment of an MRSA infection. More specifically, the approved product is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates). *See* Exhibit D; Section 1.1.

8. A compound as claimed in claim 1, wherein R^3 is a pyridinium group which may be substituted and R^4 is a hydrogen atom.

Dependent claim 8 is directed to a chemical genus encompassing the approved product (where R^1 is a phosphono group; R^2 is ethyl (i.e., a C_{1-6} alkyl group); Y is S, Q is N, X is N, n is 0; **R^3 is a pyridinium** group and R^4 is hydrogen). See Exhibit D, Section 11.

9. A compound as claimed in claim 1, wherein Q is a nitrogen atom.

Dependent claim 9 is directed to a chemical genus encompassing the approved product (where R^1 is a phosphono group; R^2 is ethyl (i.e., a C_{1-6} alkyl group); Y is S, **Q is N**, X is N, n is 0; R^3 is pyridinium group and R^4 is hydrogen). See Exhibit D, Section 11.

10. A compound as claimed in claim 1, wherein X is a nitrogen atom.

Dependent claim 10 is directed to a chemical genus encompassing the approved product (where R^1 is a phosphono group; R^2 is ethyl (i.e., a C_{1-6} alkyl group); Y is S, Q is N, **X is N**, n is 0; R^3 is pyridinium group and R^4 is hydrogen). See Exhibit D, Section 11.

11. A compound as claimed in claim 1, wherein n is 0.

Dependent claim 11 is directed to a chemical genus encompassing the approved product (where R^1 is a phosphono group; R^2 is ethyl (i.e., a C_{1-6} alkyl group); Y is S, Q is N, X is N, **n is 0**; R^3 is pyridinium group and R^4 is hydrogen). See Exhibit D, Section 11.

> 12. A method for treating a bacterial infection which comprises administering an effective amount of a compound as claimed in claim 4 to a patient suffering from the bacterial infection.

Dependent claim 12 is directed to methods of using the approved product (ceftaroline fosamil) for treating bacterial infections. The approved product is indicated for the treatment of bacterial infections (as specified in the approved package insert). *See* Exhibit D; Section 1, 2 and 11.

> 15. A method as claimed in claim 5, wherein the compound is administered by injection.

Dependent claim 15 is directed to methods of using a chemical genus encompassing the approved product for treating bacterial infections. The methods include administering the claimed genus by injection. The approved product is an injectable for the treatment of specified bacterial infections. *See* Exhibit D; Sections 1-2 and 11.

> 16. A method for treating a bacterial infection which comprises administering an effective amount of a compound as claimed in claim 4 together with at least one of pharmaceutically acceptable carriers, diluents and excipients to a patient suffering from the bacterial infection.

Dependent claim 16 is directed to methods for using the approved product (ceftaroline fosamil) for the treatment of bacterial infections. The methods include administering the approved product together with a carrier, diluent and/or excipient. The approved product is indicated for the treatment of specified bacterial infections and is administered together with a carrier, diluent and/or excipient and. *See* Exhibit D; Sections 1, 2 and 11.

> 17. A pharmaceutical composition containing the compound shown in claim 1 and at least one of pharmaceutically acceptable carriers, diluents and bulking agents.

Dependent claim 17 is directed to compositions of chemical genus encompassing the approved product. See Exhibit D, Sections 2.3 and 11.

> 18. A pharmaceutical composition containing the compound of claim 4 and at least one of pharmaceutically acceptable carriers, diluents and bulking agents.

Dependent claim 18 is directed to compositions of the approved product (ceftaroline fosamil). See Exhibit D, Sections 2.3 and 11.

> 19. A method for producing a pharmaceutical composition comprising mixing a compound of claim 4 with a pharmaceutically acceptable carrier, diluent or bulking agent.

Dependent claim 19 is directed to methods for producing compositions of the approved product (ceftaroline fosamil). See Exhibit D, Sections 2.3 and 11.

> 20. A method as claimed in claim 12, wherein the compound is administered by injection.

Dependent claim 20 is directed to methods of using the approved product for treating bacterial infections. The methods include administering the approved product by injection. The approved product is an injectable for the treatment of specified bacterial infections. *See* Exhibit D; Sections 1-2 and 11.

> 21. A method as claimed in claim 12, wherein the bacterial infection is a MRSA infection.

Dependent claim 21 is directed to methods of using the approved product for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. The approved product is indicated

for the treatment of an MRSA infection. More specifically, the approved product is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates).The approved product is indicated for the treatment of an MRSA infection (as specified in the approved package insert). *See* Exhibit D; Section 1.1.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) application or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued;

Takeda licensed the rights to develop ceftraoline fosamil to Peninsula Pharmaceuticals, Inc. (Peninsula). Peninsula filed the investigational new drug (IND) application on December 10, 2004 (Exhibit G). The IND was assigned Application No. 71,371 (Exhibit H) The IND was received by the FDA on December 13, 2004 (Exhibit H) and became effective on January 12, 2005 (thirty days after the FDA receipt date). *See* 21 U.S.C. § 355(i)(2). Peninsula transferred ownership of the IND to Cerexa, Inc. (Cerexa), a wholly-owned subsidiary of Forest Laboratories, Inc. (Forest), as of June 30, 2005 (Exhibit I), which was acknowledged by the FDA on July 14, 2005 (Exhibit J).

The NDA for ceftaroline fosamil, NDA 20-0327, was submitted to the FDA by Cerexa on December 30, 2009 (Exhibit K).

NDA 20-0327 was approved by the FDA on October 29, 2010 (Exhibit E).

A chronology of regulatory review of ceftaroline fosamil is attached as Exhibit L.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

Takeda licensed the rights to develop ceftraoline fosamil to Peninsula Pharmaceuticals, Inc. (Peninsula). Peninsula submitted an IND application for ceftaroline fosamil on December 10, 2004 (Exhibit G). The IND was assigned Application No. 71,371. The IND was received by the FDA on December 13, 2004 (Exhibit H). 21 U.S.C. § 355(i)(2) provides that clinical investigation of a drug may begin thirty days after receipt of the IND application by the FDA. The IND, therefore, became effective on January 12, 2005.

Peninsula transferred ownership of the IND to Cerexa, Inc. (Cerexa), a wholly-owned subsidiary of Forest Laboratories, Inc. (Forest), as of June 30, 2005 (Exhibit I).

On December 30, 2009, Cerexa submitted an NDA for ceftaroline fosamil, which was assigned number 20-0327 (Exhibit K). The NDA was approved on October 29, 2010 (Exhibit E). A chronology of regulatory review of ceftaroline fosamil is attached as Exhibit L. Several significant dates are also summarized below. Applicants reserve the right to supplement the activity described in Exhibit L if further clarification is needed.

DATE	*DESCRIPTION OF ACTIVITIES*
December 13, 2004	*FDA receipt of IND submission*
January 12, 2005	*IND effective date*
December 30, 2009	*NDA 200327 submitted to and received by FDA*
October 29, 2010	*FDA approves NDA 200327*

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of the extension was determined.

It is the opinion of the Applicant that the '175 patent is eligible for patent term extension under 35 U.S.C. § 156(a). The Applicant claims an extension of 1211 days, which would extend the expiration date of the '175 patent to at least April 11, 2022.

Statement of Eligibility of the Patent for Extension

Under 35 U.S.C. § 156(a)

Section 156(a) provides in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. § 156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent and in accordance with 35 U.S.C. § 156(d)(1)-(4); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) except for 35 U.S.C. §§ 156(a)(5)(B) and 156(a)(5)(C), the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

Each of these elements is satisfied:

(1) The term of the '175 patent expires on December 17, 2018. This application has, therefore, been submitted before the expiration of the patent term.

(2) The term of the '175 patent has never been extended under 35 U.S.C. § 156(e)(1).

(3) The application is submitted by Foley and Lardner LLP, attorney for Takeda, which has been appointed under a general power of attorney to act for the owner of the '175 patent for the purpose of filing this Request. This application is submitted in accordance with 35 U.S.C. § 156(d) within the sixty-day period beginning October 29, 2010 when the product received permission for marketing under the FFDCA and contains the information required under 35 U.S.C. §§ 156(d)(1)(A)-(E).

(4) The product was the subject of IND 71,371 (filed on December 10, 2004; and effective on January 12, 2005), and NDA 20-0327 (filed on December 30, 2009 and approved on October 29, 2010). Thus, the product was subject to a regulatory review period under § 505(b) of the FFDCA before its commercial marketing or use.

(5) Finally, the permission for the commercial marketing of the approved product after regulatory review under FFDCA § 505(b) is the first permitted commercial marketing of the approved product in the United States. This is confirmed by the absence of any approved NDA under which the approved product could be commercially marketed prior to October 29, 2010.

Statement as to the Length of the Extension Claimed

In Accordance with 37 C.F.R. 1.775

The term of the '175 patent should be extended by 1211 days. The extension was determined according to 37 C.F.R. § 1.775 and the PTO worksheet "Calculation of Length for Patent Term Extension for a Human Drug Product" as follows:

(1) 1814 — The number of days in the period beginning on the effective date of the IND (January 12, 2005) and ending on the date the NDA was initially submitted (December 30, 2009). This is the "testing phase" as defined in 37

		C.F.R. § 1.775(c)(1).
(2)	304	The number of days in the period beginning on the date the NDA was initially submitted (December 30, 2009) and ending on the date of NDA approval (October 29, 2010). This is the "approval phase" as defined in 37 C.F.R. § 1.775(c)(2).
(3)	2118	The sum of (1) and (2). This is the regulatory review period as defined in 37 C.F.R. § 1.775(c).
(4)	0	The number of days in the approval phase (2) which were on and before issuance of the '175 patent. 37 C.F.R. § 1.775(d)(1)(i).
(5)	0	The number of days in the approval phase (2) during which the Applicant did not act with due diligence. 37 C.F.R. § 1.775(d)(1)(ii).
(6)	0	The sum of (4) and (5).
(7)	2118	The difference between the regulatory review period (3) and (6). 37 C.F.R. § 1.775(d)(1)(ii).
(8)	0	The number of days of the period of the testing phase (1) which occurred prior to the issuance of the '175 patent. 37 C.F.R. § 1.775(d)(1)(i).
(9)	0	The number of days of the period of the testing phase (1) during which the Applicant failed to act with due diligence 37 C.F.R. § 1.775(d)(1)(ii).
(10)	0	The sum of (8) and (9).
(11)	2118	The difference between the regulatory review period (7) and (10).
(12)	1814	The number of days of the testing phase (1).
(13)	0	The number of days from (10).
(14)	1814	Subtract line (13) from line (12)
(15)	907	One half of (14) 37 C.F.R. § 1.775(d)(1)(iii)[1]
(16)	1211	Subtract line (15) from line (11)
(17)	December 17, 2018	The original expiration date of the '175patent.
(18)	April 11, 2022	The expiration date of the '175 patent if the original expiration date is extended by the number of days in line (16). 37 C.F.R. § 1.775(d)(2)

[1] 37 C.F.R. § 1.775(d)(1) provides that for purposes of subtraction, half days are ignored.

(19)	October 29, 2010	The date of approval of the application under § 505(b) of the FFDCA.
(20)	14 years	The limitation of 37 C.F.R. § 1.775(d)(3).
(21)	October 29, 2024	The number of years in (20) plus the date on (19). 37 C.F.R. § 1.775(d)(3).
(22)	April 11, 2022	The earlier of line (18) or line (21)
(23)	December 17, 2018	The original expiration date of the '175 patent.
(24)	5 years	The applicable limitation of 37 C.F.R. § 1.775(d)(5)
(25)	December 17, 2023	The number of years on (24) plus the date on (23).
(26)	April 11, 2022	The earlier of line (22) or line (25)
(27)	December 17, 2018	The original expiration date of the '175 patent
(28)	1211	The number of days which is the difference between the date on line (27) and the date on line (26)

(13) A statement that the Applicant acknowledges a duty to disclose to the Commission of Patents and Trademarks and to the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought for the '175 patent by this Request as required by 37 C.F.R. § 1.765.

(14) Prescribed Fee:

A credit card authorization form for the prescribed fee is submitted herewith. Authorization is given to charge Deposit Account 19-0741 any deficiency in fees.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed

Inquiries and correspondence relating to this Application should be directed to the registered practitioner authorized to act on behalf of the patent owner in connection with this Application:

Stephen B. Maebius
Foley & Lardner LLP
3000 K Street, N.W.
Washington, D.C. 20007-5143
Tel: 202-672-5300

(16) Certification Under 37 C.F.R. § 1.740(b)

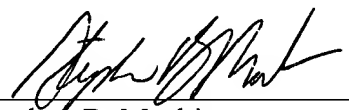
Two additional copies of this Application and Exhibits are submitted herewith in accordance with 37 C.F.R. § 1.740(b).

In view of the foregoing, Foley and Lardner LLP, acting under a general power of attorney for the patent owner, Takeda Pharmaceutical Company Limited, requests that the Commissioner grant an extension of 1211 days to U.S. Patent No. 6,417,175.

Favorable action is earnestly solicited.

Respectfully submitted,

Date Dec. 13, 2010



Stephen B. Maebius
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List of Exhibits

Exhibit 1 - Forest Laboratories, Inc. regulatory activity authorization letter in support of Application for Extension of Patent Term Under 35 USC §156.

Exhibit A - U.S. Patent No. 6,417,175

Exhibit B - Assignment of the '175 patent from the inventors to Takeda

Exhibit C - Copies of a General Power of Attorney and Statement under 37 C.F.R. 3.73(b), filed concurrently herewith, authorizing Foley and Lardner LLP to act on behalf of Takeda Pharmaceutical Company Limited.

Exhibit D - Approved package insert for TEFLARO™

Exhibit E - FDA Approval Letter

Exhibit F - Receipt showing payment of the 3½ and 7½ year maintenance fees for the '175 patent

Exhibit G - Letter dated December 10, 2004 submitting IND 71,371

Exhibit H - Letter from FDA acknowledging receipt of IND on December 13, 2004

Exhibit I - Letter dated June 30, 2005 informing FDA of transfer of IND 71,371 from Peninsula Pharmaceuticals, Inc. to Cerexa, Inc.

Exhibit J - Letter from FDA acknowledging transfer of IND from Peninsula Pharmaceuticals, Inc. to Cerexa, Inc.

Exhibit K - Letter dated December 30, 2009 submitting NDA 20-0327 to FDA

Exhibit L - Chronology of Regulatory Review of TEFLARO™ (FDA interactions; Clinical Studies; and IND/NDA submission/correspondence log)

EXHIBIT 1

Forest Laboratories, Inc.

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December 8, 2010

Mr. Yoichi Okumura
Takeda Pharmaceutical Company Limited
Intellectual Property Department
17-85, Jusohonmachi 2-Chome
Yodogawa-KU Osaka 532-8686
JAPAN

Re: Teflaro™ Approval

Dear Mr. Okumura,

Concerning the approval by the Federal Food and Drug Administration (FDA) in the United States on October 29, 2010 of NDA 200327 for Teflaro™. (NDA 200327 was submitted on December 30, 2009 and references IND No. 71,371 submitted on December 10, 2004), Cerexa, Inc. ("Cerexa"), a wholly owned subsidiary of Forest Laboratories and a sponsor of this research, confirms by this letter our prior and continuing authorization for Takeda Pharmaceutical Company Limited to rely upon the regulatory activities of Cerexa before the FDA for purposes of recently filed applications to extend the patent term of US Patent Nos. US 6,906,055 and US 6,417,175 based on the Teflaro™ approval.

Please feel free to submit this correspondence to the US Patent and Trademark Office as a confirmation of our authorization.

Sincerely,

Charles S. Ryan, J.D., Ph.D.

EXHIBIT A

US006417175B1

(12) **United States Patent**
Ishikawa et al.

(10) **Patent No.: US 6,417,175 B1**
(45) **Date of Patent: Jul. 9, 2002**

(54) **PHOSPHONOCEPHEM DERIVATIVES, PROCESS FOR THE PREPARATION OF THE SAME, AND USE THEREOF**

(75) Inventors: **Tomoyasu Ishikawa**, Otsu; **Shohei Hashiguchi**, Toyonaka; **Yuji Iizawa**, Muko, all of (JP)

(73) Assignee: **Takeda Chemical Industries, Ltd.**, Osaka (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/555,949**

(22) PCT Filed: **Dec. 17, 1998**

(86) PCT No.: **PCT/JP98/05709**

§ 371 (c)(1),
(2), (4) Date: **Jun. 6, 2000**

(87) PCT Pub. No.: **WO99/32497**

PCT Pub. Date: **Jul. 1, 1999**

(30) **Foreign Application Priority Data**

Dec. 19, 1997 (JP) 9-351499

(51) **Int. Cl.**[7] **C07D 9/6561**; A61K 31/675
(52) **U.S. Cl.** **514/80**; 540/225; 540/227
(58) **Field of Search** 540/227, 225; 514/80

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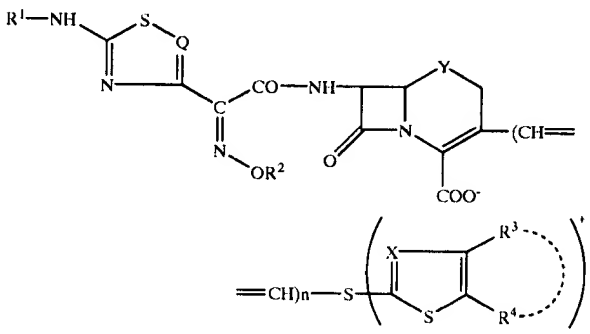
Primary Examiner—Mark L. Berch
(74) *Attorney, Agent, or Firm*—Mark Chao; Elaine M. Ramesh

(57) **ABSTRACT**

A novel cephem compound of the formula:



wherein R^1 is a phosphono group or a group convertible to a phosphono group; R^2 is a hydrogen atom or a group having a linkage through a carbon atom; each of Q and X is a nitrogen atom or CH; Y is S, O or CH_2; n is 0 or 1; one of R^3 and R^4 is a pyridinium group which may be substituted and the other is a hydrogen atom or hydrocarbon group which may be substituted, or R^3 and R^4 taken together may form a quaternalized nitrogen-containing heterocyclic ring which may be substituted, or its ester or its salt, which has a superior anti-bacterial activity, stability, absorbability, etc., a production thereof and a pharmaceutical composition containing it, is provided.

21 Claims, No Drawings

PHOSPHONOCEPHEM DERIVATIVES, PROCESS FOR THE PREPARATION OF THE SAME, AND USE THEREOF

This application is the National Stage of International Application No. PCT/JP98/05709, filed on Dec. 17, 1998.

TECHNICAL FIELD

This invention relates to a novel cephem compound having excellent antibacterial activities on a broad range of Gram-positive and Gram-negative bacteria, especially *Staphylococus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA) and a bacteria belonging to Pseudomonas and being sufficiently water-soluble, to a method of producing the compound and to a medicine, especially an antibacterial composition containing the compound.

BACKGROUND ART

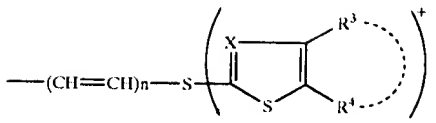
Various cephem compounds having, at the 7-position, 2-(5-amino-1,2,4-thiadiazole -3-yl)-2(Z)-alkoxyiminoacetamido group, and having, at the 3-position, 3- or 4-(pyridinium) thiazole-4-ylthio group or condensed heterocyclic ring-thio group containing N^+ as a ring constituting atom, have been reported in JPA H9(1997)-100283. However these compounds are not sufficiently soluble in water, and it is preferable to use solubilizing, agents when these compounds are dissolved in water. Thus these compounds are sufficiently satisfactory when they are used in a pharmaceutical preparation, especially for injection.

And various cephem compounds having, at the 7-position, 2-(5-phosphonoamino-1,2,4thiadiazole-3-yl)-2(Z)-methoxyiminoacetamido group, and having at the 3-position, a substituted methyl, i.e., pyridiniummethyl group or 1-methylpyridiniumthiomethyl group which are different from substituted —(CH=CH)$_n$—S-group in chemical structure, have also been reported in JPA S59(1984)-31791.

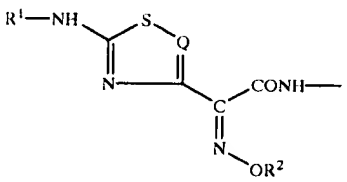
Though some recently developed cephalosporin compounds have sufficient activity against methicillin-resistant staphylococcus aureus (MRSA), they are poorly soluble in water or physiologically acceptable saline, which is necessary for administration, and have not been put into practical use. Thus creation of novel compounds, overcoming these problems has been desired.

DISCLOSURE OF INVENTION

Taking the foregoing circumstances into consideration, the present inventors diligently conducted extensive studies and synthesized, for the first time, a cephem compound characterized by having, at the 3-position of its cephem, oxacephem or carbacephem nucleus, a group of the formula:



wherein one of R^3 and R^4 is a pyridinium group which may be substituted and the other is a hydrogen atom or hydrocarbon group which may be substituted, or R^3 and R^4 taken together may form a quaternalized nitrogen-containing heterocyclic ring which may be substituted; X is a nitrogen atom or CH; and n is 0 or 1, and, at the 7-position, a group of the formula:

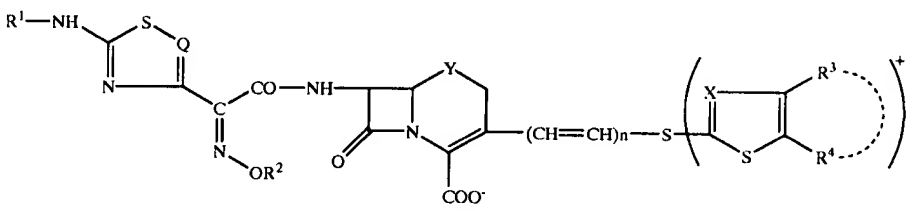


wherein R^1 is a phosphono group or a group convertible to a phosphono group; R^2 is a hydrogen atom or a group having a linkage through a carbon atom; Q is a nitrogen atom or CH, or an ester or salt thereof, and further found that the compound thus synthesized showed good solubility to water and has excellent medicinal properties such as antibacterial activity.

Based on these findings, the present invention was accomplished.

More specifically, the present invention relates to.

(1) A compound of the formula:



(I)

wherein R^1 is a phosphono group or a group convertible to a phosphono group; R^2 is a hydrogen atom or a group having a linkage through a carbon atom; each of Q and X is a nitrogen atom or CH; Y is S, O or CH_2; n is 0 or 1; one of R^3 and R^4 is a pyridinium group which may be substituted and the other is a hydrogen atom or hydrocarbon group which may be substituted, or R^3 and R^4 taken together may form a quaternalized nitrogen-containing heterocyclic ring which may be substituted, salt or ester thereof;

(2) A compound according to the above (1), wherein R^1 is a phosphono group which may be protected;

(3) A compound according to the above (1), wherein R^1 is phosphono, dialkoxy-phosphoryl, O-alkyl-phosphono, diaminophosphoryl, (amino)(hydroxy)phosphoryl, (alkoxy)(morpholino)phosphoryl or dihalophosphoryl;

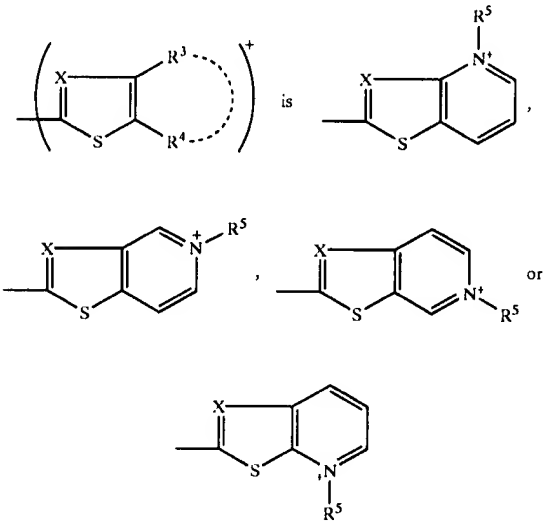
(4) A compound according to the above (1), wherein R^1 is a phosphono group;

(5) A compound according to the above (1), wherein y is S;

(6) A compound according to the above (1), wherein R^2 is a C_{1-6}alkyl group which may be substituted or a C_{3-5}cycloalkyl group;

(7) A compound according to the above (1), wherein R^3 is a pyridinium group which may be substituted and R^4 is a hydrogen atom;

(8) A compound according to the above (1), wherein



wherein R^5 is a hydrocarbon group which may be substituted;

(9) A compound according to the above (1) wherein Q is a nitrogen atom;

(10) A compound according to the above (1), wherein X is a nitrogen atom;

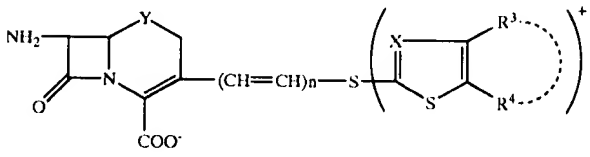
(11) A compound according to the above (1), wherein n is 0;

(12) A compound according to the above (1), which is 7β-[2(Z)-ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazole-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate, its ester or its salt;

(13) A compound according to the above (1), which is 7β-[2(Z)-fluoromethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazole-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio)-3-cephem-4carboxylate, its ester or its salt;

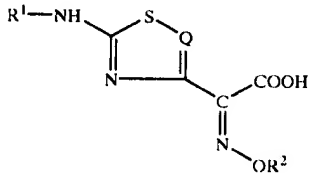
(14) A method for producing a compound shown in the above (1) which comprises reacting a compound of the formula:

(II)



wherein each symbol has the meaning given above, its ester or its salt, with a compound of th e formula:

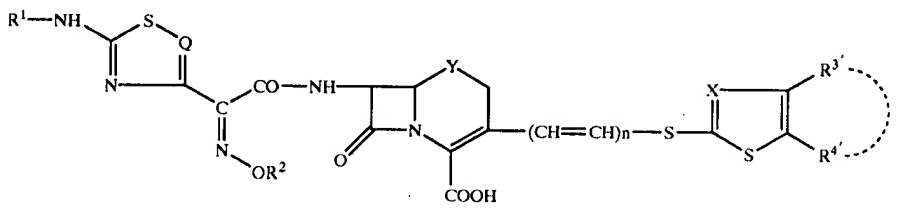
(III)



wherein each symbol has the meaning given above, its salt or its reactive derivative, if necessary, followed by converting R^1 to a phosphono group;

(15) A method for producing a compound shown in the above (1) which comprises subjecting a compound of the formula:

(IV)



wherein one of $R^{3'}$ and $R^{4'}$ is a pyridyl group which may be substituted, and the other is a hydrogen atom or a hydrocarbon group which may be substituted, or $R^{3'}$ and $R^{4'}$, taken together, represent a nitrogen-containing heterocyclic ring which may be substituted, and the other symbols have the meanings given above, its ester or its salt to the nitrogen quaternalization reaction in which quaternalized-ammonium is formed, if necessary, followed by converting R^1 to a phosphono group;

(16) A pharmaceutical composition containing the compound as shown in the above (1);

(17) A pharmaceutical composition containing the compound shown in the above (1) and at least one of pharmaceutically acceptable carriers, diluents and bulking agents;

(18) A pharmaceutical composition as shown in the above (16) which is an anti-bacterial composition;

(19) A pharmaceutical composition as shown in the above (16) which is an anti-MRSA agent;

(20) A pharmaceutical composition as shown in the above (16) which is an injectable composition;

(21) Use of the compound as shown in the above (1) for producing a pharmaceutical composition;

(22) Use as shown in the above (21), wherein the pharmaceutical composition is an antibacterial agent;

(23) Use as shown in the above (21), wherein the pharmaceutical composition is an anti-MRSA agent;

(24) Use as shown in the above (21), wherein the pharmaceutical composition is an injectable composition;

(25) A method for treating a bacterial infection which comprises administering an effective amount of a compound as shown in the above (1) to a patient suffering from the bacterial infection;

(26) A method for treating a bacterial infection which comprises administering an effective amount of a compound as shown in the above (1) together with at least one of pharmaceutically acceptable carriers, diluents and excipients to a patient suffering from the bacterial infection;

(27) A method as shown in the above (25), wherein the bacterial infection is a MRSA infection; and

(28) A method as shown in the above (25), wherein the compound is administered by injection.

BEST MODE FOR CARRYING OUT THE INVENTION

The cephem compound in the present specification includes a group of compounds named on the basis of "cepham" disclosed in "The Journal of The American Chemical Society" Vol. 84, p.3400 (1962), which means a compound, among the cepham compounds, having a double bond at the 3, 4-positions.

Incidentally, the compounds of this invention include the compound of the formula (I) showing the free form or an ester or salt thereof (a salt of the compound (I) or a salt of the ester of the compound (I)). In the present specification, hereinafter, unless otherwise specified, the compound of the formula (I) shown in the free form or an ester or salt thereof is simply referred to as the compound (I) or the antibacterial compound (I). Accordingly, the compound (I) in the present specification includes, usually, the free form as well as an ester or salt thereof.

R^1 is a phosphono group or a group convertible to a phosphono group. The group convertible to a phosphono group is a group which can be converted to a phosphono group, for example, by hydrolysis, substitution reaction, etc. Examples of the group convertible to phosphono group include, for example, dihalophosphoryl such as di-chlorophosphoryl, etc. in addition to a protected-phosphono group.

The protected-phosphono group is a phosphono group protected by a phosphono-protective group. In the field of nucleic acid, phosphono-protective groups have been sufficiently studied, and the method of a protecting phosphono group has been established. In the present invention also, conventional phosphono-protective groups can be adequately employed. Examples of protected-phosphono groups include mono-or di-ester phosphono group (e.g., dihalophosphoryl such as di-chlorophosphoryl, etc.; dialkoxy-phosphoryl group such as di-methoxyphosphoryl, di-ethoxyphosphoryl, di-propoxyphosphoryl, etc.; O-alkyl-phosphono group such as O-methyl phosphono, O-ethyl phosphono, etc.), mono-esterified mono-amidated phosphono group (e.g., mono-or di-amidated phosphono group such as diaminophosphoryl, (amino)(hydroxy) phosphoryl, etc.; (alkoxy)(amino)phosphoryl group such as (methoxy)(amino)phosphoryl, (ethoxy)(amino)phosphoryl, etc.; (alkoxy)(morpholino)phosphoryl group such as (methoxy)(morpholino)phosphoryl, (ethoxy)(morpholino) phosphoryl, etc.), etc. As R^1, phosphono, dialkoxy-phosphoryl, O-alkyl-phosphono, diaminophosphoryl, (amino)(hydroxy)phosphoryl, (alkoxy)(morpholino) phosphoryl or dihalophosphoryl are preferable, and phosphono is the most preferable.

R^2 is a hydrogen atom or a group having a linkage through a carbon atom. Examples of the group having a linkage through a carbon atom represented by R^2 include, for example, a hydrocarbon group which may be substituted (for example, an alkyl group which may be substituted, an alkenyl group which may be substituted, an alkynyl group which may be substituted, an aralkyl group which may be substituted, a cyclic hydrocarbon group which may be substituted), an acyl group or a non-aromatic heterocyclic group (having linkage at a carbon atom) which may be substituted. Among them, an alkyl group which may be substituted, an alkenyl group which may be substituted, a cyclic hydrocarbon group which may be substituted etc. are preferable. As the alkyl group in "an alkyl group which may be substituted", a C_{1-6}alkyl group, etc., are preferable, and methyl, ethyl, isopropyl, etc. are the most preferable. As the alkenyl group in "an alkenyl group which may be substituted", a C_{2-6}alkenyl group is preferable. As the alkynyl group in "an alkynyl group which may be substituted", a C_{2-6}alkynyl group is preferable. As the aralkyl group in "an aralkyl group which may be substituted", a C_{7-20}aralkyl group is preferable. Examples of the cyclic hydrocarbon group in "a cyclic hydrocarbon group which may be substituted" include, a 3 to 7 membered non-aromatic cyclic hydrocarbon group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclopentene-1-yl, 3-cyclopentene-1-yl, 2-cyclohexene-1-yl, 3-cyclohexene-1-yl, etc., etc. Among them, a C_{3-7}cycloalkyl group such as cyclobutyl, cyclopentyl, etc. are preferable. Examples of the acyl group include, for example, a C_{1-6}alkanoyl group which may be substituted, a C_{3-5}alkenoyl group which may be substituted, a C_{6-10}aryl-carbonyl group which may be substituted, a heterocyclic carbonyl group, etc.

As the "optionally substituted C_{1-6}alkanoyl group", use is made of, for example, a C_{1-6}alkanoyl group which may optionally be substituted with 1 to 3 substituents selected from a halogen, oxo, a C_{1-6}alkoxy, a C_{1-6}alkanoyl, a C_{6-10}aryl, a C_{6-10}aryloxy, and a C_{6-10}arylthio. More specifically, use is made of, for example, formyl, acetyl, propionyl, butyryl, valeryl, pivaloyl, succinyl, glutaryl, monochloroacetyl, dichloroacetyl, trichloroacetyl, monobromoacetyl, monofluoroacetyl, difluoroacetyl, trifluoroacetyl, monoiodoacetyl, acetoacetyl, 3-oxobutyryl, 4-chloro-3-oxobutyryl, phenylacetyl, p-chlorophenylacetyl, phenoxyacetyl and p-chlorophenoxyacetyl.

As the "optionally substituted C_{3-5}alkenoyl group", use is made of, for example, a C_{3-5}alkenoyl group optionally substituted with 1 to 3 substituents selected from a halogen and a C_{6-10}aryl, more specifically, for example, acryloyl, crotonoyl, maleoyl, cinnamoyl, p-chlorocinnamoyl and β-phenylcinnamoyl.

As the "optionally substituted C_{6-10}aryl-carbonyl group", use is made of, for example, al C_{6-10}aryl-carbonyl group optionally substituted with 1 to 3 substituents selected from a halogen, nitro, hydroxy, a C_{1-6}alkyl and a C_{1-6}alkoxy, more specifically, for example, benzoyl, naphthoyl, phthaloyl, p-toluoyl, p-tert-butylbenzoyl, p-hydroxybenzoyl, p-methoxybenzoyl, p-tert-butoxybenzoyl, p-chlorobenzoyl and p-nitrobenzoyl.

The "heterocyclic group" in "heterocyclic carbonyl group" means a group formed by removing one hydrogen atom linked to carbon atom of the heterocyclic ring. The heterocyclic ring means a 5- to 8-membered ring containing 1 to several, preferably 1 to 4 hetero-atoms such as a nitrogen atom which may be oxidized, oxygen atom and a sulfur atom, or a condensed ring thereof. As such a heterocyclic group, for example, 2- or 3-pyrrolyl; 3-, 4- or 5-pyrazolyl; 2-, 4- or 5-imidazolyl; 1,2,3- or 1,2,4-triazolyl; 1H- or 2H-tetrazolyl; 2- or 3-furyl; 2- or 3-thienyl; 2-, 4- or 5-oxazolyl; 3, 4- or 5-isoxazolyl; 1,2,3-oxadiazol-4-yl or 1,2,3-oxadiazol-5-yl; 1,2,4-oxadiazol-3-yl or 1,2,4-oxadiazol-5-yl; 1,2,5- or 1,3,4-oxadiazolyl; 2-, 4- or 5-thiazolyl; 3-, 4- or 5-isothiazolyl; 1,2,3-thiadiazol-4-yl or 1,2,3-thiadiazol-5-yl; 1,2,4-thiadiazol-3-yl or 1,2,4-thiadiazol-5-yl; 1,2,5- or 1,3,4-thiadiazolyl; 2- or 3-pyrrolidinyl; 2-, 3- or 4-pyridyl; 2-, 3- or 4-pyridyl-N-oxido; 3- or 4-pyridazinyl; 3- or 4-pyridazinyl-N-oxido; 2-, 4- or 5-pyrimidinyl; 2-, 4- or 5-pyrimidinyl-N-oxido; pyrazinyl; 2-, 3- or 4-piperidinyl; piperazinyl; 3H-indol-2-yl or 3H-indol-3-yl; 2-, 3- or 4-pyranyl; 2-, 3- or 4thiopyranyl; benzopyranyl; quinolyl; pyrido[2,3-d]pyrimidyl; 1,5-, 1,6-, 1,7-, 1,8-, 2,6- or 2,7-naphthyridyl; thieno[2,3-d]pyridyl; pyrimidopyridyl; pyrazinoquinolyl; and benzopyranyl can be used.

Examples of the non-aromatic heterocyclic group in "non-aromatic heterocyclic group having a linkage at a carbon atom, which may be substituted" preferably include a 3 to 6 membered non-aromatic heterocyclic group containing 1 or 2 hetero atoms such as a nitrogen atom, an oxygen atom, a sulfur atom in addition to a carbon atom, such as oxylanyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl.

Examples of the substituents, which the above-mentioned "hydrocarbon group" may optionally have, include a heterocyclic group, a hydroxyl group, a C_{1-6}alkoxy group, a C_{3-10}cycloalkyl group, a C_{3-7}cycloalkyloxy group, a C_{6-10}aryloxy group, a C_{7-19}aralkyloxy group, a heterocyclic-oxy group, a mercapto group, a C_{1-6}alkylthio group, a C_{3-10}cycloalkylthio group, a C_{6-10}arylthio group, a C_{7-19}aralkylthio group, a heterocyclic-thio group, an amino group, a mono-C_{1-6}alkylamino group, a di-C_{1-6}alkylamino group, a tri-C_{1-6}alkyl ammonium group, a C_{3-10}cycloalkylamino group, a C_{6-10}arylamino group, a C_{7-19}aralkylamino group, a heterocyclic amino group, a cyclic amino group, an azido group, a nitro group, a halogen atom, a cyano group, a carboxyl group, a C_{1-10}alkoxy-carbonyl group, a C_{1-10}aryloxy-carbonyl group, a C_{7-19}aralkyloxy-carbonyl group, a C_{6-10}aryl-carbonyl group, a C_{1-6}alkanoyl group, a C_{3-5}alkenoyl group, a C_{6-10}aryl-carbonyloxy group, a C_{2-6}alkanoyloxy group, a C_{3-5}alkenoyloxy group, an optionally substituted carbamoyl group, an optionally substituted thiocarbamoyl group, an optionally substituted carbamoyloxy group, a phthalimido group, a C_{1-6}alkanoylamino group, a C_{6-10}aryl-carbonylamino group, a C_{1-10}alkoxy-carboxamido group, a C_{6-10}aryloxy-carboxamido group and a C_{7-19}aralkyloxy-carboxamido group. The number of these substituents, which may be the same as or different from one another, ranges from 1 to 4.

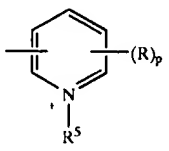
Among specific examples of the above-mentioned substituents of the "hydrocarbon group", as the "optionally substituted carbamoyl group", use is made of, for example, a carbamoyl group and a cyclic aminocarbonyl group optionally substituted with one or two substituents selected from, for example, a C_{1-6}alkyl group, a C_{6-10}aryl group, a C_{1-6}alkanoyl group, a C_{6-10}arylcarbonyl group and a C_{1-6}alkoxy-phenyl group. More specifically, use is made of, for example, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-phenylcarbamoyl, N-acetylcbrbamoyl, N-benzoylcarbamoyl, N-(p-methoxyphenyl)carbamoyl, pyrrolidinocarbonyl, piperidinocarbonyl, piperazinocarbonyl and morpholinocarbonyl. As the "optionally substituted thiocarbamoyl group", use is made of a thiocarbamoyl group optionally substituted with one or two substituents selected from[f]or example, a C_{1-6}alkyl group and a C_{6-10}aryl group, which are exemplified by thiocarbamoyl, N-methylthiocarbamoyl and N-phenylthiocarbamoyl. As the "optionally substituted calrbamoyloxy group", use is made of a carbamoyloxy group optionally substituted with one or two substituents selected from[f]or example, a C_{1-6}alkyl group and a C_{6-10}aryl group. Specific examples include carbamoyloxy, N-methyl carbamoyloxy, N,N-d(methyl carbamoyloxy, N-ethyl carbamoyloxy and N-phenyl carbamoyloxy.

As the heterocyclic group and the heterocyclic group in the heterocyclic-oxy group, the heterocyclic-thio group and the heterocyclic amino group in the substituent of the "hydrocarbon group", use is made of group;similar to those in the "heterocyclic carbonyl group" as mentioned above.

Examples of the substituent in the "non-aromatic heterocyclic group having a linkage at a carbon atom, which may be substituted" mentioned above include the embodiments mentioned as the hydrocarbon group and its substituent in the "hydrocarbon group which may be substituted".

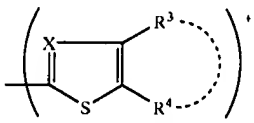
As R^2, an optionally substituted hydrocarbon group is preferable. Examples of the "optionally substituted hydrocarbon group" shown by R^3include a C_{1-6}alkyl group optionally substituted with one to three substituents selected from, for example, a hydroxyl group, a C_{3-10}cycloalkyl group, a C_{1-6}alkoxy group, a C_{1-6}alkylthio group, an amino group, a halogen atom, carboxyl group, a C_{1-10}alkoxycarbonyl group, an optionally substituted carbamoyl group, a cyano group, an azido group and a heterocyclic group, which are more specifically exemplified by cyclopropylmethyl, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 1-ethoxyethyl, 2-hydroxyethyl, methylthiomethyl, 2-aminoethyl, fluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, chloromethyl, 2-chloroethyl, 2,2-dichloroethyl, 2,2,2-trichloroethyl, 2-bromoethyl, 2-iodoethyl, 2,2,2-trifluoroethyl, carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 2-carboxypropyl, 3-carboxypropyl, 1-carboxybutyl, cyanomethyl, 1-carboxy-1-methylethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-methoxycarbonyl-1-methylethyl, 1-ethoxycarbonyl-1-methylethyl, 1-tert-butoxycarbonyl-1-methylethyl, 1-benzyloxycarbonyl-1-methylethyl, 1-pivaloyloxycarbonyl-1-methylethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, 2-azidoethyl, 2-(pyrazolyl)ethyl, 2-(imidazolyl)ethyl, 2-(2-oxopyrrolidin-3-yl)ethyl and 1-carboxyl-1-(2,3,4-trihydroxyphenyl)methyl. Most preferable examples of R^2 include, for example, a straight chain or branched C_{1-6}alkyl group which may be substituted with one to three substituents selected from a halogen, a hydroxyl a C_{1-6}alkoxy group, a carboxyl group, a C_{1-10}alkoxy-carbonyl group, a cyano group, a carbamoyl group and a substituted carbamoyl, such as methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, fluoromethyl, 2-fluoroethyl, 2-chloroethyl, 2-hydroxyethyl, 2-methoxyethyl, cyanomethyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, etc., a C_{3-5}cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, etc. and a C_{3-5}cycloalkyl-C_{1-3}alkyl group such as cyclopropylmethyl, etc. Among them, a C_{1-6}alkyl group which may be substituted and C_{3-5}cycloalkyl group are preferable.

One of $R^3$and R^4 is a pyridinium group which may be substituted and the other is a hydrogen atom or a hydrocarbon group which may be substituted, or R^3 and R^4, taken together, represent a heterocyclic group which may be substituted containing a quaternalized nitrogen. Examples of the "pyridinium group which may be substituted" include, for example, a group of the formula:

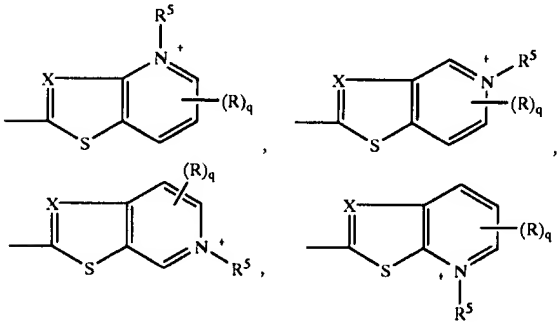


wherein R^5 is a hydrocarbon group which may be substituted, R is a C_{1-6}alkyl group, a C_{1-6}alkoxy group, a C_{1-6}alkoxy-carbonyl group, a amino group, a nitro group, a halogen atom or a carboxy group, p is an integer of from 0 to 4, etc.

In case that R^3 and R^4, taken together, represent a heterocyclic group containing a quaternalized nitrogen, which may be substituted, the group of the formula:



includes 6 membered unsaturated heterocyclic groups such as



wherein q is an integer of 0 to 3, and the other symbols have the meanings given above, etc.

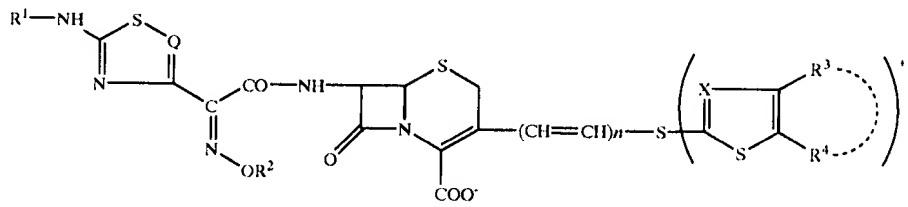
Examples of the "hydrocarbon group which may be substituted" represented by R^3, R^4 or R^5 include those mentioned in the explanation of "a group having a linkage through a carbon atom" represented by R^2.

Each of p and q is preferably 0.

R^5 is preferably is a C_{1-4}alkyl group such as methyl, etc. Referring to R^3 and R^4, it is preferable that R^3 is a pyridinium group which may be substituted and R^4 is a hydrogen atom, or that R^3 and R^4, taken to represent a 6 membered unsaturated heterocyclic group having a quaternalized nitrogen atom.

Each of Q and X is a nitrogen atom or CH. Each of Q and X is preferably a nitrogen atom.

Y is S, O or CH_2. Y is preferably S. That is, among the compound (I), a compound of the formula:



(I')

wherein each symbol has the meaning given above, its ester or its salt is preferable. While n can be 0 or 1, it is preferably 0.

In the above-mentioned compound (I), the mark [—] attached on the right shoulder of —COO at the 4-position shows that the carboxyl group forms carboxylate anion, making a pair with the positive charge on the pyridine ring (hereinafter sometimes simply referred to as A^+). On the other hand, the compound (I) may optionally form a pharmaceutically acceptable ester or salt. As the pharmaceutically acceptable salt, use is made of, for example, inorganic basic salts, ammonium salts, organic basic salts, inorganic acid addition salts, organic acid addition salts and basic amino acid salts. As the inorganic base capable of forming the inorganic basic salt, use is made of, for example, alkali metal (e.g. sodium and potassium) and alkaline earth metals (e.g. calcium); as the organic base capable of forming the organic basic salt, use is made of, for example, procaine, 2-phenylethyl benzylamine, dibenzylethylenediamine, ethanolamine, diethanolamine, trishydroxymethylaminomethane, polyhydroxyalkylamine and N-methylglucosamine; as an inorganic acid capable of forming the inorganic acid addition salt, use is made of, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid; as an organic acid capable of forming the organic acid addition salt, use is made of, for example, p-toluenesulfonic acid, methanesulfonic acid, formic acid, trifluoroacetic acid and maleic acid; and, as a basic amino acid capable of forming the basic amino acid salt, use is made of, for example, lysine, arginine, ornithine and histidine. Among these salts, a basic salt (i.e. an inorganic basic salt, an ammonium salt, an organic basic salt and a basic amino acid salt) means that capable of being formed in the case where a basic group such as amino group, a monoalkylamino group, a dialkylamino group, a cycloalkylamino group, an arylamino group, an aralkylamino group, a cyclic amino group and a N-containing heterocyclic group exists in the substituent R^1, R^2 or R^5 of the compound (I). And, examples of the acid addition salt include a salt in which the substituent at 4-position is a carboxyl group (COOH) and the substituent at 3-position is $—(CH=CH)_n—S—A^+Z^-$ [wherein Z^- stands for anion formed by removing proton H^+ from the inorganic acid or the organic acid, the anion being exemplified by a chloride ion, a bromide ion, a sulfate ion, a p-toluenesulfonate ion, a methanesulfonate ion and a trifluoroacetate ion, etc.] the salt being formed by adding one mole of acid to the moiety forming the internal salt of the compound (I), i.e. the carboxylate moiety (COO^-)

at the 4-position and heterocyclic ring moiety at the 3-position. The ester derivative of the compound (I) means an ester producible by esterifying the carboxyl group in the molecule which is utilizable as an intermediate of the synthesis and is metabolically unstable and a non-toxic ester. Examples of the ester utilizable as intermediate of the synthesis include an optionally substituted C_{1-6}alkyl ester, a C_{1-6}alkyl ester, a C_{3-10}cycloalkyl ester, a C_{3-10}cycloalkyl-C_{1-6}alkyl ester, an optionally substituted C_{6-10}aryl ester, an optionally substituted C_{7-12}aralkyl ester, a di-C_{6-10}aryl-methyl ester, a tri-C_{6-10}aryl-methyl ester, a substituted silyl ester and a C_{2-6}alkanoyloxy-C_{1-6}alkyl ester.

As the "optionally substituted C_{1-6}alkyl ester", use is made of, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl and n-hexyl, which may be substituted with one to three of, for example, benzyloxy, a C_{1-4}alkyl sulfonyl (e.g. methyl sulfonyl), trimethylsilyl, a halogen (e.g. fluorine, chlorine and bromine), acetyl, nitrobenzoyl, mesylbenzoyl, phthalimido, succinimide, benzenesulfonyl, phenylthio, a di-C_{1-4}alkylamino (e.g. dimethylamino), pyridyl, a C_{1-4}alkyl sulfinyl (e.g. methyl sulfinyl) and cyano. Examples of such groups include benzyloxymethyl, 2-methylsulfonylethyl, 2-trimethylsilylethyl, 2,2,2-trichloroethyl, 2-iodoethyl, acetylmethyl, p-nitrobenzoylmethyl, p-mesylbenzoylmethyl, phthalimidomethyl, succinimidomethyl, benzenesulfonylmethyl, phenylthiomethyl, dimethylaminoethyl, pyridine-oxido-2-methyl, methylsulfinylmethyl and 2-cyano-1,1-dimethylethyl.

As the C_{2-6}alkenyl group forming the "C_{2-6}alkenyl ester", use is made of, for example, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, methallyl, 1,1-dimethylallyl and 3-methyl-3-butenyl.

As the C3-10cycloalkyl group forming the "C_{3-10}cycloalkyl ester", use is made of, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl and adamantyl.

As the C_{3-10}cycloalkyl -C_{1-6}alkyl group forming the "C_{3-10}cycloalkyl-C_{1-6}alkyl ester", use is made of, for example, cyclopropylmethyl, cyclopentylmethyl and cyclohexylmethyl.

As the "C_{6-10}aryl group" forming the "optionally substituted C_{6-10}aryl ester", use is made of, for example, phenyl, α-naphthyl, β-naphthyl and biphenylyl, which may optionally be substituted with one to three of, for example, nitro and a halogen (e.g. fluorine, chlorine and bromine). The above group is specifically exemplified by p-nitrophenyl and p-chlorophenyl.

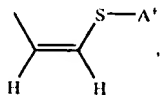
As the "C_{7-12}aralkyl group" forming the "optionally substituted C_{7-12}aralkyl ester", use is made of, for example, benzyl, 1-phenylethyl, 2-phenylethyl, phenylpropyl and naphthylmethyl, which may optionally be substituted with one to three of, for example nitro, a C_{1-4}alkoxy (e.g. methoxy), a C_{1-4}alkyl (e.g. methyl and ethyl) and hydroxy. Specific examples of such group include p-nitrobenzyl, p-methoxybenzyl and 3,5-di-tert-butyl-4-hydroxybenzyl.

As the di-C_{6-10}aryl-methyl group forming the "di-C_{6-10}aryl-methyl ester", use is made of, among others, benzhydryl; as the tri-C_{6-10}aryl-methyl group forming the tri-C_{6-10}aryl-methyl ester, use is made of, among others, trityl; as the substituted silyl group forming the substituted silyl ester, use is made of, for example, trimethylsilyl, tert-butyldimethylsilyl and $—Si(CH_3)_2CH_2CH_2Si(CH_3)_2—$. As the C_{2-6}alkanoyloxy-C_{1-6}alkyl ester, use is made of, for example, acetoxymethyl ester. Examples of the above-mentioned ester include an ester at 4-position. The compound, wherein the substituent at 4-position is the above-mentioned ester group, forms a salt in which the substituent at 3-position is $—(CH=CH)_n—S—A^+Z^-$ [wherein symbols are of the same meaning as defined above].

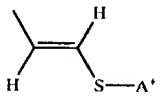
The present invention includes, besides the above-described ester derivatives, pharmacologically acceptable compounds convertible into the compound (I) in vivo.

The compound (I) and starting compounds of this invention, in case that n is 1, include cis-isomer (Z-compound), trans-isomer (E-compound) and a cis-trans mixture. The compound (I) of this invention is preferably a trans-isomer (E-compound).

Referring to the compound (I), the cis-isomer (Z-compound), for example, means one of the geometrical isomers having the partial structure represented by the formula:



and the trans-isomer means a geometrical isomer having the partial structure of the formula:



Among the compound (I), for example, 7β-[2(Z)-ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazole-3-yl) acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate, its ester, its salt, 7β-[2(Z)-fluoromethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazole-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate, its ester and its salt, are especially preferable.

In the present specification, specific examples of the respective substituents are, unless specifically described, as follows.

halogen: fluoro, chloro, bromo, iodo, etc.;

C_{1-4}alkyl group: methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, etc.;

C_{1-6}alkyl group: the above mentioned C_{1-4}alkyl group and pentyl, 2,2-dimethyl propyl, hexyl, etc.;

C_{2-6}alkenyl group: vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, methallyl, 1,1-dimethyl allyl, etc.;

C_{2-6}alkynyl group: ethynyl, 1-propynyl, 2-propynyl, 2-butynyl, 2-pentynyl, 2-hexynyl, etc.;

C_{3-5}cycloalkyl group: cyclopropyl, cyclobutyl, cyclopentyl, etc.;

C_{3-10}cycloalkyl group: the above mentioned C_{3-5}cycloalkyl group and cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, etc.;

C_{6-10}aryl group: phenyl, naphthyl, etc.;

C_{7-20}aralkyl group: benzyl, l-phenyl ethyl, 2-phenyl ethyl, phenyl propyl, naphthyl methyl, benzhydryl, etc.;

C_{1-6}alkoxy group: methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, 2,2-dimethyl propyloxy, hexyloxy, etc.;

C_{3-7}cycloalkyloxy group: cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, etc.;

C_{6-10}aryloxy group: phenoxy, naphthyloxy, etc.;

C_{7-19}aralkyl-oxy group: benzyloxy, 1-phenylethyloxy, 2-phenylethyloxy, benzhydryloxy, etc.;

C_{1-6}alkyl-thio group: methylthio, ethylthio, propylthio, butylthio, isobutylthio, t-butylthio, pentylthio, 2,2-dimethylpropylthio, hexylthio, etc.;

C_{3-10}cycloalkyl-thio group: cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, cycloheptylthio, cyclooctylthio, cyclodecylthio, etc.;

C_{6-10}aryl-thio group: phenylthio, naphthylthio, etc.;

C_{7-19}aralkyl-thio group: benzylthio, phenylethylthio, benzhydrylthio, tritylthio, etc.;

C_{1-4}alkyl-sulfinyl group methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, t-butylsulfinyl, etc.;

C_{1-4}alkyl-sulfonyl group: methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, t-butylsulfonyl, etc.;

mono-C_{1-6}alkyl-amino group: methylamino, ethylamino, n-propylamino, n-butylamino, etc.;

di-C_{1-4}alkyl-amino group dimethylamino, diethylamino, methylethylamino, di-(n-propyl)amino, di-(n-butyl) amino, etc.;

di-C_{1-6}alkyll-amino group: the above mentioned di-C_{1-4}alkyl amino group and di-(pentyl)amino, di-(n-hexyl)amino, etc.;

tri-C_{1-6}alkyl-ammonium group trimethylammonium, etc.;

C_{3-10}cycloalkyl-amino group cyclopropylamino, cyclopentylamino, cyclohexylamino, etc.;

C_{6-10}aryl-amino group: anilino, N-methylanilino, etc.;

C_{7-19}aralkyl-amino group: benzylamino, 1-phenylethylamino, 2-phenylethyl amino, benzhydrylamino, etc.;

Cyclic amino group: pyrrolidino, piperidino, piperazinyl, morpholino, 1-pyrrolyl, etc.;

C_{1-6}alkanoyl amino group: acetamido, propionamido, butyroamido, valeroamido, pivaloamido, etc.;

C_{6-10}aryl-carbonyl amino group benzamido, naphthoylamido, phthalimide, etc.;

C_{1-6}alkanoyl group: formyl, acetyl, propionyl, butyryl, valeryl, pivaloyl, succinyl, glutaryl, etc.;

C_{2-6}alkanoyloxy group: acetoxy, propionyloxy, butyryloxy, valeryloxy, pivaloyloxy, etc.;

C_{3-5}alkenoyl group: acryloyl, crotonoyl, maleoyl, etc.;

C_{3-5}alkenoyl-oxy group: acryloyloxy, crotonoyloxy, maleoyloxy, etc.;

C_{6-10}aryl-carbonyl group benzoyl, naphthoyl, phthaloyl, phenyl acetyl, etc.;

C_{6-10}aryl-carbonyloxy group: benzoyloxy, naphthoyloxy, phenylacetoxy, etc.,

C_{1-6}alkoxy-phenyl group: methoxyphenyl, ethoxyphenyl, propoxyphenyl, butoxy phenyl, t-butoxyphenyl, etc.;

C_{1-10}alkoxy-carbonyl group: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, 2,2-dimethylpropyloxycarbonyl, hexyloxycarbonyl, heptyloxycarbonyl, decyloxycarbonyl, etc.;

C_{2-10}alkenyloxy-carbonyl group allyloxycarbonyl, etc.;

C_{6-10}aryloxy-carbonyl group: phenoxycarbonyl, naphthyloxycarbonyl, etc.;

C_{7-19}aralkyl-oxycarbonyl group: benzyloxycarbonyl, benzhydryloxycarbonyl, etc.;

C_{1-10}alkoxy-carboxamido group methoxycarboxamido (CH_3OCONH—), ethoxycarboxamido, tert-butoxycarboxamido, etc.;

C_{6-10}aryloxy-carboxamido group: phenoxycarboxamido (C_6H_5OCONH—), etc.

Methods of producing the compound (I) of this invention are hereinafter described in detail.

Production Method (1):

The compound (I) can be synthesized by allowing, for example, a compound of the formula (II) or an ester or salt thereof (hereinafter referred to as Compound (II)) to react with a compound of the formula (III) or its salt or a reactive derivative thereof (hereinafter referred to as Compound (III)), followed by removing the protective group so as to change the group R^1 to a phosphono group.

The present method is to acylate a compound (II) by using compound (III). Compound (II) can be used as it is, and can also be used as its salt or its ester.

Examples of the salts of Compound (II) include an inorganic basic salt, an ammonium salt, an organic basic salt, an inorganic acid addition salt and an organic acid addition salt. Examples of inorganic basic salts include an alkali metal salt (e.g. sodium salt and potassium salt) and an alkaline earth metal salt (e.g. calcium salt); examples of an organic basic salt include trimethylamine salt, triethylamine salt, tert-butyldimethylamine salt, dibenzylmethylamine salt, benzyldimethylamine salt, N,N-dimethylaniline salt, pyridine salt and quinoline salt; examples of the inorganic acid addition salts include hydrochloride, hydrobromide, sulfate, nitrate and phosphate; and examples of the organic acid addition salts include formate, acetate, trifluoroacetate, methanesulfonate and p-toluenesulfonate.

As the ester of amino compound (II), mention is made of esters already described as the ester derivatives of compound (I), as exemplified by, more specifically, a C_{1-6}alkyl ester, a C_{2-6}alkenyl ester, a C_{3-10}cycloalkyl ester, a C_{3-6}cycloalkyl-C_{1-6}alkyl ester, a C_{6-10}aryl ester, a C_{7-12}aralkyl ester, a di-C_{6-10}arylmethyl ester, a tri-C_{6-10}arylmethyl ester and a C_{2-6}alkanoyloxy-C_{1-6}alkyl ester.

Compound (II) can be produced by the method shown in, for example, JPA-H9(1997)-100283, etc.

In this method, Compound (III) in the free state or in the form of a salt or reactive derivative thereof can be used as an agent for acylating the amino group at the 7-position of Compound (III). Examples of the salts of Compound (III) includes inorganic basic salts and organic basic salts. Examples of inorganic basic salts include alkali metal salts (e.g. sodium salt and potassium salt) and alkaline earth metal salts (e.g. calcium salt); examples of the organic basic salts include trimethylamine salt, triethylamine salt, tert-butyldimethylamine salt, dibenzylmethylamine salt, benzyldimethylamine salt, N,N-dimethylaniline salt, pyridine salt and quinoline salt.

In this method, the compound (III) as it is, its salt or its reactive derivative is used as an acylating agent for acylation of the amino group at the 7-position of amino compound. Examples of the salt of compound (III) include an inorganic base salt and an organic base salt. Examples of the inorganic base salt include alkali metal salt (e.g. sodium salt, potas-

sium salt, etc.), alkaline earth metal salt (e.g., calcium salt, etc.), etc., and examples of the organic base salt include trimethylamine salt, triethylamine salt, tert-butyl dimethylamine salt, dibenzyl methylamine salt, benzyl dimethylamine salt, N,N-dimethyl aniline salt, pyridine salt, quinoline salt etc. Examples of the reactive derivative of the carboxylic acid (III) include, for example, acid halides, acid azides, acid anhydrides, mixed acid anhydrides, active amides, active esters, active thio esters, etc. Examples of the acid halides include, for example, acid chloride, acid bromide, etc.; examples of the mixed acid anhydrides include mono-C_{1-6}alkyl-carbonic acid mixed acid anhydrides (e.g. mixed acid anhydride of free acid and monomethylcarbonic acid, monoethylcarbonic acid, monoisopropylcarbonic acid, mono-isobutylcarbonic acid, mono-tert-butylcarbonic acid, mono-benzylcarbonic acid, mono-(p-nitrobenzyl)carbonic acid, mono-allylcarbonic acid, etc.), a C_{1-6}aliphatic carboxylic acid mixed acid anhydride (e.g. mixed acid anhydride of free acid and acetic acid, trichloroacetic acid, cyanoacetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, pivalic acid, trifluoroacetic acid, trichloroacetic acid, acetoacetic acid, etc.),a C_{7-12} aromatic carboxylic acid mixed acid anhydride (e.g. mixed acid anhydride of free acid and benzoic acid, p-toluic acid, p-chloro benzoic acid, etc.), organic sulfonic acid mixed acid anhydrides (e.g. mixed acid anhydride of free acid and methanesulfonic acid, ethane sulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.) etc.; examples of the active amide include an amide with a nitrogen-containing heterocyclic compound (acid amide of a free acid and, for example; pyrazole, imidazole, benzo triazole, etc., these nitrogen-containing heterocyclic compound may be substituted with a C_{1-6}alkyl group (e.g., methyl, ethyl, etc.), a C_{1-6}alkoxy group (e.g., methoxy, ethoxy, etc.), a halogen atom (e.g., fluorine, chlorine, bromine, etc.), an oxo group, a thioxo group, a C_{1-6}alkylthio group (e.g., methylthio, ethylthio, etc.), etc.), etc.

As an active ester, all the active esters used in the field of the synthesis of β-lactam and peptide may be used. Examples of the active ester include, for example, an organic phosphoric acid ester (e.g. di-ethoxyphosphoric acid ester, di-phenoxyphosphoric acid ester, etc.), p-nitrophenyl ester, 2,4-di-nitrophenyl ester, cyanomethyl ester, pentachlorophenyl ester, N-hydroxysuccinimide ester, N-hydroxy phthalimide ester, 1-hydroxy benzotriazole ester, 6-chloro-1-hydroxybenzotriazole ester, 1-hydroxy-1H-2-pyridone ester, etc. Examples of the active thio ester include an ester of the acid with an aromatic heterocyclic thiol compound (e.g. 2-pyridylthiol ester, 2-benzothiazolylthiol ester, etc., which heterocyclics may be substituted with a C_{1-6}alkyl group (e.g. methyl, ethyl, etc.), a C_{1-6}alkoxy group (e.g., methoxy, ethoxy, etc.), a halogen atom (e.g., fluorine, chlorine, bromine, etc.), a C_{1-6}alkyl-thio group (e.g., methylthio, ethylthio, etc.), etc.).

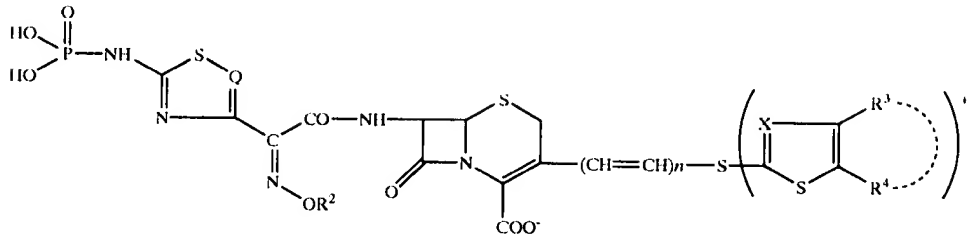
The Compound (III) may easily be produced by a known method (e.g. a method shown in JPA S60(1985)-231684, JPA S62(1987)-149682, EP0590681, etc.) or a method similar to the known method. The reaction derivative of Compound (III) can be reacted with Compound (II) after isolation from the reaction mixture, and the reaction mixture containing the reactive derivative of Compound (III) can also be used for the reaction with Compound (II). When Compound (III) is used in the form of a free acid or a salt, a pertinent condensing agent is used. Excamples of the condensing agent include, for example, a N,N'-disubstituted carbodiimide such as N,N'-dicyclohexylcarbodiimide, etc., an azolide reagent such as N,N'-carbonyldiimidazole, N,N'-thiocarbonyldiimidazole, etc., a dehydrating agent such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, an alkoxy-acetylene, etc., a 2-halogeno pyridinium salt such as 2-chloropyridiniummethyl iodide, 2-fluoropyridiniummethyl iodide, etc. When these condensing agents are used, the reaction proceeds through a reactive derivative of Compound (III). The reaction is usually carried out in a solvent which does not interfere with the reaction. Examples of the solvent include, for example, an ether such as dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisoprpyl ether, ethylene glycol-dimethyl ether, etc , an ester such as ethyl formate, ethyl acetate, acetic acid n-butyl, etc., a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, trichlene, 1,2-dicholoroethane, etc., a hydrocarbon such as n-hexane, benzene, toluene, etc., an amide such as formamide, N,N-dimethylformamide, N,N-dimethylacetamido, etc., a ketone such as acetone, methylethylketone, methylisobutylketone, etc., a nitrile such as acetonitrile, propionitrile, etc., dimethylsulfoxide, sulfolane, hexamethylphosphoramide, water, etc. These solvents may be used alone or in combination of two or more.

The amount of Compound (III) used is usually 1 to 5 moles, preferably about 1 to 2 moles per mole of Compound (II). The reaction is usually conducted in a temperature of from about −80 to 80° C., preferably from about −40 to 50° C., more preferably from about −30 to 30° C. The reaction time varies depending upon the kind of Compound (II) and Compound (III), the kind of solvent used (ratio of a solvent in case of using a mixed solvent) and the reaction temperature, and is usually about 1 minute to 72 hours, preferably about 15 minutes to 3 hours. When an acid halide is used as the acylating agent, the reaction may be carried out in the presence of a acid scavenger in order to eliminate from the reaction system a hydrogen halide formed by the reaction.

Examples of the acid scavenger include, for example, an inorganic base such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydrogen carbonate, etc., a tertiary amine such as triethylamine, tri-(n-propyl) amine, tri-(n-butyl)amine, diisopropylethylamine, cyclohexyldimethylamine, pyridine, lutidine, γ-collidine, N,N-dimethylaniline, N-methyl piperidine, N-methylpyrrolidine, N-methylmorpholine, etc., an alkylene oxide such as propylene oxide, epichlorohydrin etc., etc. In case that R^1 is a hydrogen atom and a phosphono group is introduced when the reaction derivative forms, the reaction mixture containing reaction product wherein R^1 is a dihalophosphoryl group, may be deprotected by treating with water to obtain a compound (I) wherein R^1 is a phosphono group, or may be treated with an an alkanol such as methanol, ethanol, etc., to obtain a compound (I) wherein R^1 is an esterified phosphono group.

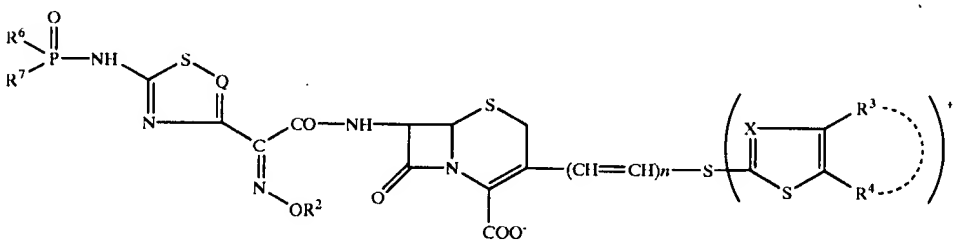
Production Method (2):

Among Compound (I), a compound of the formula:



(Ia)

wherein each symbol has the meaning given above, or salt thereof (hereinafter sometimes referred to as Compound (Ia)) can be produced by subjecting a compound of the formula:



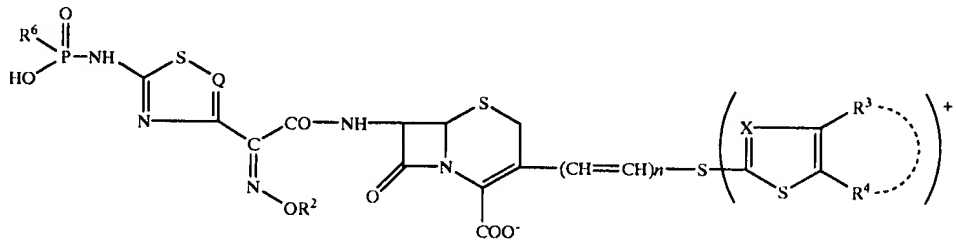
(Ib)

wherein R^6 and R^7 represent, the same or different, a protecting group of phosphono group, the other symbols have the meanings given above, or a salt thereof (hereinafter sometimes referred to as Compound (Ib)) to the deprotection reaction so that the protected phosphono group is deprotected.

Examples of the protecting group of a phosphono group represented by R^6 or R^7 include, for example, a halogen (e.g. chlorine atom, etc.), an alkoxy (e.g., a C_{1-3}alkoxy group such as methoxy, ethoxy, propoxy, etc.), amino, morpholino, thiomorpholino, etc.

The present method can be carried out, for example, by reacting Compound (Ib) with a halogenated trimethylsilyl such as trimethylsilyl bromide, trimethylsilyl iodide, trimethylsilyl chloride, etc., a metal halide such as sodium iodide, potassium iodide, sodium bromide, etc., an alkali metal thiocyanate such as sodium thiocyanate, potassium thiocyanate, etc., etc. The reaction is carried out in a solvent which does not interfere with the reaction, though examples of the preferable solvent include methylene chloride, dimethylacetamide, etc. The reaction temperature is not limiting and the reaction is carried out usually under cooling or under mild conditions like slight heating.

When R^6 and R^7 in Compound (Ib) are different, a protecting group of only one of R^6 and R^7 in Compound (Ib) can be removed by selecting the reaction condition. In this case, compound of the formula:



(Ic)

wherein each symbol has the meaning given above, or salt thereof (hereinafter sometimes referred to as Compound (Ic)) is obtained.

Production Method (3):

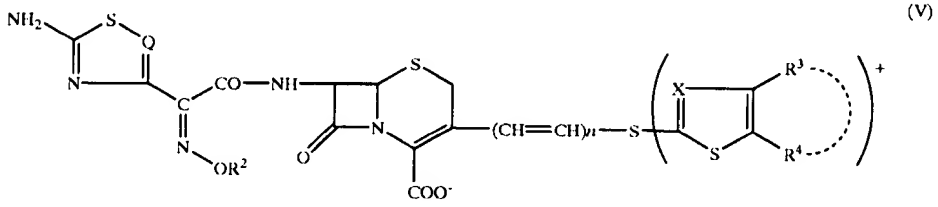
Compound (Ia) can be produced, for example, by subjecting Compound (Ic) to a deprotecting reaction for removing the protecting group of the phosphono group.

The present method can be carried out, for example, by treating Compound (Ic) with an acid. The acid may be an organic acid or an inorganic acid. Preferable examples of the acid include, for example, formic acid, sulfuric acid, trifluoroacetic acid, benzenesulfonic acid, nitric acid, p-toluenesulfonic acid, hydrochloric acid, etc. More preferable examples of the acid include, for example, formic acid, trifluoroacetic acid, hydrochloric acid, etc. The acid suitable for the reaction is selected by taking the group which is

hydrolyzed into consideration. The reaction can be carried out with or without a solvent. Examples of the suitable solvent include an organic solvent, water, mixed solvent thereof, etc., which is usually used as a solvent. When trifluoroacetic acid is used, the reaction is preferably carried out in the presence of anisole.

Production Method (4)

Compound (I) can be produced by condensing a compound of the formula:



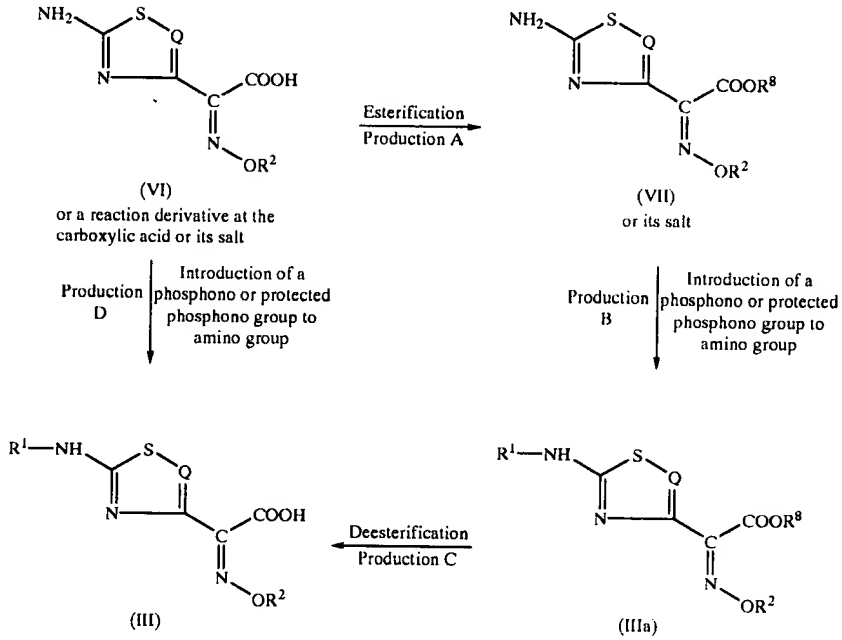
(V)

wherein each symbol has the meaning given above, or a salt thereof (hereinafter sometimes referred to as Compound (V)) and a phosphoric acid derivative.

The reaction can be carried out by using Compound (V) or a salt thereof and a phosphorus halide such as phosphorus trichloride, phosphorus pentachloride, etc., etc. The reaction is usually carried out in a solvent such as a halogenated alkylene (e.g. methylene chloride, ethylene chloride, etc.), toluene, etc. The reaction temperature is not limiting and the reaction is carried out usually under cooling, an ambient temperature or under mild conditions like slight heating. In this reaction, when the reaction mixture contains:Compound (I) wherein R^1 is dihalophosphoryl group, the reaction mixture may further be treated either with water to give Compound (I) wherein R^1 is phosphono group or with an alcohol (alkanol such as methanol, ethanol, etc.) to give Compound (I) wherein R^1 is an esterified phosphono group.

Compound (I) produced by the above production methods (1) to (4) can be isolated and purified by known methods, for example, extraction, column chromatography, precipitation, recrystallization, etc. On the other hand, isolated Compound (I) can be converted to a physiologically acceptable salt by a known method.

The method for producing the starting compound (III) is explained as follows:



Production A

In the above formulas; R^8 is the ester part of the esterified carboxylic group represented by the formula: CO_2R^8.

A compound of the formula (VII) or salt (hereinafter referred to sometimes as Compound (VII)) can be produced by subjecting a compound of the formula (VI), its reactive derivative or its salt (hereinafter sometimes referred to as Compound (VI)) to esterification.

Examples of the preferable salts of Compound (VI) include, for example, a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), ammonium salt, an organic salt such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, di-cyclohexylamine salt, N,N'-dibenzyl amine salt, etc., etc. Preferable examples of the reactive derivatives at carboxylic acid of Compound (VI) include those mentioned for Compound (III).

Examples of the esterifying agent used in the esterification reaction include a compound of the formula:

$(R^8)_2SO_4$, R^{8a}—N_2 or R^8—X^1

wherein R^8 has the meaning given above, R^{8a} is a group removed a hydrogen atom from R^8, X^1 is hydroxy or a halogen.

Preferable examples of the halogen include chlorine, bromine, iodine and fluorine.

In case that a sulfuric acid ester and an alkyl halide are used as the esterifying agent, while the reaction is usually carried out in a solvent such as water, acetone, methylene chloride, ethanol, ether, dimethylformamide, etc., the reaction can be carried out in any solvent which does not interfere with the reaction. The reaction is preferably carried out in the presence of the inorganic base or the organic base mentioned above. The reaction temperature is not limiting but the reaction is usually carried out under cooling or under heating which is not higher than the boiling point of the solvent used.

In case that a diazo compound is used as the esterifying agent, the reaction is usually carried out in the presence of ether, tetrahydrofuran, etc., the reaction temperature is not limiting but the reaction is usually carried out under cooling or at an ambient temperature.

Preferable examples of the salts of Compound (VII) include, an acid addition salt such an organic acid salt as acetic acid salt, maleic acid salt, tartaric acid salt, benzenesulfonic acid salt, toluenesulfonic acid salt, etc., such inorganic acid salt as hydrochloric acid salt, hydrobromic acid salt, sulfuric acid salt, phosphoric acid salt, etc.

Productions B and D

A compound of the formula (III), its reactive derivatives at the carboxylic acid or its salt (hereinafter referred to as Compound (III)) and a compound of the formula (IIIa), its reactive derivatives at the carboxylic acid or its salt (hereinafter referred to as Compound (IIIa)) can be produced by introducing a phosphono group to the amino group of Compound (VI) and Compound (VII), respectively. Preferable examples of the reactive derivatives at the carboxylic acid of Compound (VI) and Compound (VII) include those mentioned for Compound (III).

Examples of the introducing agents to be used in the introduction reaction include, an phosphorus halide such as phosphorus trichloride, phosphorus pentachloride, etc., phosphorus oxychloride, etc. The reaction is usually carried out in a solvent such as a halogenated alkylene (e.g. methylene chloride, ethylene chloride, etc.) toluene, ethyl acetate, tetrahydrofuran, etc.

In this reaction, the reaction mixture containing Compound (III) or Compound (IIIa), wherein R^1 is a dihalophosphoryl group, which is obtained by reacting Compound (VI) or Compound (VI) with the above mentioned introducing agent such as a phosphorous halide, can be treated with water to give a reaction mixture containing Compound (III) or (IIIa) wherein R^1 is a phosphono group, or can treated with an alcohol such an alkanol as methanol, ethanol, etc. to give a reaction mixture containing Compound (III) or Compound (IIIa) wherein R^0 is an esterified phosphono group.

The reaction product (III) or (IIIa) wherein R^0 is a dihalophosphoryl group can be isolated from the above mentioned reaction mixture by means of a conventional isolation method. The product can be used in the following reaction.

The reaction includes changing Compound (IIIa) to the reactive derivative at the carboxylic group.

Production C

Compound (III) can be produced by subjecting Compound (IIIa) to deesterification reaction.

Preferable examples of the salt of Compound (III) include those enumerated for Compound (VI).

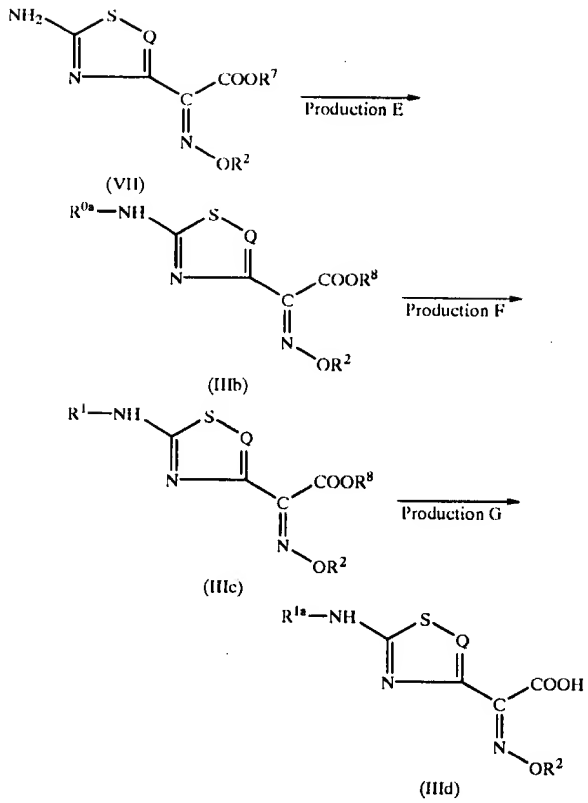
The reaction is carried out by a conventional method such as hydrolysis, reduction, etc. The hydrolysis is preferably carried out in the presence of a base or an acid. Preferable examples of the base include an inorganic base and an organic base such as an alkali metal (e.g. sodium, potassium, etc.), an alkaline earth metal (e.g. magnesium, calcium, etc.), hydroxide, carbonate, bicarbonate of the above mentioned metal, an trialkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, 1,5-di-azabicyclo[4.3.0]nona-5-ene, 1,4-di-azabicyclo[2,2,2]octane, 1,8-di-azabicyclo[5.4.0]undecane, etc.

Preferable examples of the acid include an organic acid such as formic acid, acetic acid, propionic acid, trifluoroacetic acid, etc., an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, etc. Trifluoroacetic acid is preferably used in the presence of a -carbocation stabilizing agent such as anisole, etc.

While the reaction is usually carried out in water, methylene chloride, tetrahydrofuran, an alcohol (e.g. methanol, ethanol, etc.) or a mixture thereof, a solvent which does not interfere with the reaction may be used. A liquid base or an acid may also be used as a solvent. The reaction temperature is not limiting and the reaction is carried out usually under cooling or under mild conditions like slight heating.

The reduction can be applied to deprotection of a protecting group of the ester, such as 4-nitrobenzyl, 2-iodoethyl, 2,2,2-trichloro ethyl, etc. As the method of the reduction which is applied to the deesterification reaction, there may be mentioned a method using a metal such as zinc, zinc amalgam, etc., or a chromium compound salt such as chromous chloride salt, chromous acetate salt, etc., in combination with an organic or inorganic salt such as acetic acid, propionic acid, hydrochloric acid, etc., and a catalytic reduction method using a metal catalyst such as palladium-carbon, etc.

The production of a starting compound that is a compound of the formula (IIId) or its reactive derivative (hereinafter referred to as Compound (IIId)) is as follows.



[wherein R^{0a} is a dihalophosphoryl group, R^{1a} is a phosphono group which may be protected. (The definition of R^{1a} is the same as that of R^1, but R^{1a} and R^1 may be the same as or different from each other.

Production E

A compound of the formula (IIIb), its reactive derivative or its salt (hereinafter referred to as Compound (IIIb)) can be produced by subjecting Compound (VII) to a reaction in which a dihalophosphoryl group is introduced to the amino group of Compound (VII). The reaction can be carried out in a similar manner to Production B or Production D.

Production F

A compound of the formula (IIIc), its reactive derivative or its salt (hereinafter referred to as Compound (IIIc)) can be produced by subjecting Compound (IIIb) to a reaction in which the dihalophosphoryl group is converted to a phosphono group other than dihalophosphoryl group. The reaction can be carried out by subjecting Compound (IIIb) to an esterification reaction and/or amidation reaction.

The esterification reaction is carried out by reacting Compound (IIIb) with an alcohol. Preferable examples of the alcohol include methanol, ethanol, propanol, butanol, etc. The amidation reaction can be carried out by reacting Compound (IIIb) with an amine. Preferable examples of the amine include ammonia, a primary amine such as methylamine, ethylamine, etc., a secondary amine such as morpholine, dimethylamine, etc., etc.

While the esterification reaction or amidation reaction is usually carried out in a solvent such as a halogenated alkylene (e.g. methylene chloride, ethylene chloride, etc.), tetrahydrofuran, water, etc., it can be carried out in any solvent which does not interfere with the reaction. The reaction temperature is not limiting though the reaction is carried out usually under cooling or an ambient temperature.

Production G

Compound (IIId) can be produced by subjecting Compound (IIIc) to deesterification reaction.

The reaction is carried out in a similar manner to that of Production C.

In the reactions mentioned above, when the starting compound has an amino group and/or a carboxyl group, these groups may be protected by a protecting group which is conventionally used in the field of peptide chemistry, and the protecting group may be removed after the reaction.

Examples of the protecting group for the amino group include, for example, a formyl group, a C_{1-6}alkyl-carbonyl group (for example, acetyl, ethylcarbonyl, etc.), a benzyl group, a tert-butyloxycarbonyl group, a benzyloxycarbonyl group, a 9-fluorenyl methyloxycarbonyl group, an allyloxy-carbonyl group, a phenylcarbonyl group, a C_{1-6}alkyl-carbonyl group (for example, methoxycarbonyl, ethoxycarbonyl, etc.), a C_{7-10}aralkyl-carbonyl group (for example, benzylcarbonyl, etc.), a trityl group, phthaloyl group, a N,N-dimethylaminomethylene group, etc. These groups may be substituted by 1 to 3 of a halogen atom (for example, fluorine, chlorine, bromine, etc.), a nitro group, etc. Examples of the protecting group for the carboxyl group include, for example, a C_{1-6}alkyl group (for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), a phenyl group, a silyl group, a benzyl group, an allyl group, etc. These groups may be substituted by one to three of a halogen atom (for example, fluorine, chlorine, bromine, etc.), a nitro group, etc.

Examples of the protecting group for the hydroxy include, for example, a methoxy methyl group, an allyl group, a tert-butyl group, a C_{7-10}aralkyl group (for example, benzyl, etc.), formyl group, a C_{1-6}alkyl-carbonyl group (for example, acetyl, ethylcarbonyl, etc.), a benzoyl group, a C_{7-10}aralkyl-carbonyl group (for example, benzylcarbonyl, etc.), a pyranyl group, a furanyl group, a tri-alkyl silyl group, etc. These groups may be substituted by 1 to three of a halogen atom (for example, fluorine, chlorine, bromine, etc.), a C_{1-6}alkyl group (for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), a phenyl group, a C_{7-10}aralkyl group (for example, benzyl, etc.), a nitro group, etc.

As the method for the deprotection of these protecting group, a method using, for example, an acid, a base, reduction, ultraviolet ray, hydrazine, phenyl hydrazine, sodium N-methyl di-thiocarbamate, tetrabutyl ammonium fluoride, palladium acetate, etc. can be applied, using known or similar methods. When a compound is obtained as a free form in each reaction process, the compound can be converted to its salt, and when the compound is obtained as a salt, it can be converted to its free form or to an another salt.

Compound (I) thus obtained can be isolated from the reaction mixture and purified by a known procedure such as phase transfer, concentration, solvent extraction, fractional distillation, crystallization, recrystallization, chromatography, etc. When Compound (I) of the present invention exists in the form of diastereomer, conformer, etc., Compound (I) can be isolated and purified by a isolation procedure or a purification procedure mentioned above., if desirable. When Compound (I) is a racemate, (d)-form and (l)-form of Compound (I) can be isolated by a usual optical resolution procedure.

Compound (I) of the present invention has a solubility higher than that of the corresponding compound having an aminothiazolyl group wherein the amino group is free form (that is Compound (I) wherein R^1 is an amino group), and Compound (I) of the present invention in vivo, gives a

corresponding compound having an aminothiazolyl group by removing group R^1. Further Compound (I) is superior in an anti-bacterial activity to a compound having aminothiazolyl group.

The compound (I) of this invention has broad spectrum antibacterial activity and low toxicity, and can be used safely for prophylaxis and therapy of various diseases, in man and mammals (e.g. mouse, rat, rabbit, dog, cat, cow and pig), caused by pathogenic bacteria, for example, respiratory infection and urinary tract infection. Characteristic features of the antibacterial spectrum of the antibacterial compound (I) are as follows, among others:

(1) showing a remarkably high activity against a variety of Gram-negative bacteria,

(2) having high activities against Gram-positive bacteria (e.g. *Staphylococcus aureus* and *Corynebacterium diphtheriae*),

(3) having high activities against methicillin-resistant *Staphylococcus aureus* (MRSA), and

(4) having high activities also against a number of β-lactamase-producing Gram-negative bacteria (e.g. genera Escherichia, Enterobacter, Serratia and Proteus).

The anti-bacterial compound (I) of the present invention has superior stability and effectiveness of anti-bacterial activity in comparison with Compound (V).

Though the drug of the present invention may comprise only Compound (I) itself, it is usually prepared by a conventional manner by using a proper amount of pharmaceutically acceptable carriers, diluents and bulking agents, etc. which are selected from exipients (for example, calcium carbonate, kaolin, sodium hydrogen carbonate, lactose, D-mannitol, starch, crystalline cellulose, talc, fine granulated sugar, porous substance, etc.), binders (for example, dextrin, gums, α-starch, gelatine, hydroxypropylcellulose, hydroxy propyl methyl cellulose, pullulan, etc.), thickeners (for example, a natural gum, a cellulose derivative, an acrylic acid derivative, etc.), disintegrators (for example, carboxymethylcellulose calcium, crosscarmelose sodium, crospovidone, a low-substituted hydroxypropylcellulose, partly pregelatinized starch, etc.), solvents (for example, water for injection, alcohol, propylene glycol, Macrogol, sesame oil, corn oil, etc.), dispersants (for example, Tween 80, HCO60, poly ethylene glycol, carboxymethylcellulose, sodium alginate, etc.), solubilizing agents (for example, polyethylene glycol, propylene glycol, D-mannitol, benzoic acid benzyl, ethanol, tris amino methane, triethanolamine, sodium carbonate, citric acid sodium, etc.), suspending agents (for example, stearyl triethanolamine, sodium lauryl sulfate, benzalkonium chloride, polyvinyllcohol, polyvinylpyrolidone, hydroxymethylcellulose, etc.), soothing agents (for example, benzyl alcohol, etc.), isotonic agents (for example, sodium chloride, glycerin, etc.), buffer agents (for example, phosphoric acid salt, acetic acid salt, carbonic acid salt, citric acid salt, etc.), lubricants (for example, magnesium stearate, calcium stearate, talc, starch, sodium benzoate, etc.), coloring agents (for example, tar pigment, caramel, ferric oxide, titanium oxide, riboflavins, etc.), corrigents (for example, a sweetning agent, a perfume, etc.), stabilizers (for example, sodium sulfite, ascorbic acid, etc.) and preservatives (for example, paraben, sorbic acid, etc.), etc.

The pharmaceutical composition of the present invention which may contain pharmaceutically acceptable carriers, diluents, bulking agents, etc., mentioned above contains an effective amount of Compound (I) of the present invention for the treatment and prevention of bacterial infectious disease. The amount of Compound (I) contained in the pharmaceutical preparation of the present invention is usually 0.1 to 100 weight % of the pharmaceutical preparation. The pharmaceutical preparation of the present invention may contain pharmaceutically active ingredients other than Compound (I)(e.g. antitumor agents, etc., mentioned below). The amount of the pharmaceutically active ingredient other than Compound (I) is not limited as long as the aim of the present invention can be achieved. Examples of the preparation includes tablets (including a sugar-coated tablet, a film-coated tablet), pills, capsules (including microcapsule), granules, fine granules, powders, drop infusions, syrups, emulsions, suspensions, injections, aerosols, ointments, suppositories, troches, cataplasms, sustained release preparations, etc. These preparations can be prepared by a conventional method (e.g., a method shown in The Pharmacopoeia of Japan The Twelfth Edition, etc.).

As carriers for injectable preparations, use is made of, for example, distilled water or a physiological saline solution. Carriers for capsules, powdery preparations, granular preparations or tablets are used as a mixture with known pharmaceutically acceptable excipients (e.g. starch, maltose, sucrose, calcium carbonate or calcium phosphate), binders (e.g. starch, gum arabic, carboxymethyl cellulose, hydroxypropyl cellulose or crystalline cellulose), lubricants (e.g. magnesium stearate or talc) and disintegrants (e.g. carboxymethyl calcium and talc).

The compound (I) of this invention can be administered, like known penicillin preparations or cephalosporin preparations, non-orally or orally as injectable preparations, capsules, tablets or granular preparations (injectable preparations are especially preferable). The daily dose ranges from 0.5 to 80 mg, preferably from 2 to 40 mg relative to 1 kg of the body weight of a man or an animal infected with pathogenic bacteria as described above, which may be administered in two to three divided doses.

Incidentally, the medicinal composition and antibacterial composition employed in the present specification may contain the compound (I) alone, or contain, among others, such carriers as set forth above, or contain a proper amount of any other adequate antibacterial compound.

The present invention will be illustrated in further detail in the following Working Examples, which are mere examples and do not limit this invention, and may be modified within the range not deviating from the scope of this invention.

Elutions in the column chromatography conducted in Working Examples were carried out while monitoring with TLC (Thin Layer Chromatography). In the TLC monitoring, as the TLC plate, use was made of $60F_{254}$ manufactured by Merck & Co., Inc., as the developing solvent, use was made of the same solvent as employed for eluting in the column chromatography, and the detection was conducted with a UV detector. The silica gel (70 to 230 mesh) for the column was Kieselgel 60 manufactured by Merck & Co. Inc. ODS-AM is produced by YMC Co. Ltd., Dowex50W is produced by The Dow Chemical Company and Diaion HP-2OSS and SP-207 are produced by Mitsubishi Chemical Industries, Ltd.

NMR spectra were measured using tetramethylsilane as an internal or external standard with a spectrometer Gemini 200 and all delta values were expressed in ppm. The value shown in () for a mixed solvent is a mixing ratio in volume of constituent solvents. The percent (%) for a solution indicates the number of grams in 100 ml of the solution. And, the symbols in Reference Examples and Working Examples have the following meaning.

s	: singlet
d	: doublet
t	: triplet
q	: quartet
ABq	: AB type quartet
dd	: double doublet
m	: multiplet
bs	: broad singlet
J	: coupling constant

WORKING EXAMPLE 1

7β-[2(Z)-Ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate

Under ice-cooling, the pH of a solution of 7β-amino-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate hydrochloride (1.55 g) in a mixture of THF (50 ml) and H_2O (50 ml) was adjusted to 7.4 with 0.6M $NaHCO_3$. To the solution was added portionwise 2-(5-dichlorophosphorylamino-1,2,4-thiadiazol-3-yl)-2(Z)-ethoxyiminoacetyl chloride (3.69 g), and the mixture was stirred at 5° C. for 10 minutes while maintaining the pH to 7.2 to 7.3 by addition of 0.6M $NaHCO_3$. A solution of sodium acetate (861 mg) in H_2O (10 ml) was poured into the reaction mixture, and the resulting mixture was stirred at room temperature for 2.5 hours. During the stirring, the pH of the mixture was maintained above 4.5 by the occasional addition of 0.6M $NaHCO_3$ (total volume 56 ml). After the pH of the mixture was adjusted to 3.0 with 1N HCl (4 ml), the reaction mixture was concentrated under reduced pressure. The concentrate was diluted with H_2O (800 ml) and purified by MCI gel HP-20SS column chromatography (500 ml: eluents=H_2O 1.5L, 10% aq EtOH 0.5L, 20% aq EtOH 1.5L). The fractions containing the desired compound were concentrated under reduced pressure, and the concentrate was lyophilized to give the crude titled compound (1.64 g).

^1H NMR (D_2O) δ: 1.33 (3H,t,J=7.2 Hz), 3.56, 3.94 (2H,ABq,J=17.2 Hz), 4.34 (3H,s), 4.35 (2H,q,J=7.2 Hz), 5.38 (1H,d,J=5 Hz), 5.90 (1H,d,J=5 Hz), 8.34, 8.72 (each 2H,d,J=6.6 Hz), 8.51 (1H,s); IR (KBr, cm^{-1}): 3055, 1778, 1682, 1643, 1520, 1385, 1190, 1038.

WORKING EXAMPLE 2

7β-[2(Z)-Ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate

The crude lyophilized compound (1.54 g) obtained in Working Example 1 was dissolved in a solution of $NaHCO_3$ (378 mg) in H_2O (16 ml). The solution was subjected to ODS-AM column chromatography (450 ml: eluents=1N HCl 4.5 ml, H_2O 0.1L, 5% aq acetonitrile 0.5L, 20% aq acetonitrile 0.25L). The fractions containing the desired compound were concentrated under reduced pressure, and the concentrate was lyophilized to give the titled compound (431 mg).

Anal Calcd for $C_{22}H_{21}N_8O_8PS_4.2.0H_2O$: C, 36.66; H, 3.50; N, 15.55. Found: C, 36.70; H, 3.94; N, 15.53.

WORKING EXAMPLE 3

7β-[2(Z)-Fluoromethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate

Under ice-cooling, the pH of a solution of 7β-amino-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate hydrochloride (1.42 g) in a mixture of THF (50 ml) and H_2O (50 ml) was adjusted to 7.5 with 0.6M $NaHCO_3$ (12 ml). To the solution was added portionwise 2-(5-dichlorophosphorylamino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoxyiminoacetyl chloride (3.41 g), and the mixture was stirred at 5° C. for 10 minutes while maintaining the pH to 7.2 to 7.5 by addition of 0.6M $NaHCO_3$ (24 ml). A solution of sodium acetate (787 mg) in H_2O (20 ml) was poured into the reaction mixture, and the resulting mixture was stirred at room temperature for 3 hours. After the pH of the mixture was adjusted to 3.0 with 1N HCl (3.4 ml), the reaction mixture was concentrated under reduced pressure. The concentrate was diluted with H_2O (750 ml) and purified by MCI gel HP-20SS column chromatography (500 ml: eluents=H_2O 1.5L, 10% aq EtOH 0.5L, 20% aq EtOH1.5L). The fractions containing the desired compound were concentrated under reduced pressure, and the concentrate was lyophilized to give the crude titled compound (0.96 g).

^1H NMR (D_2O) δ: 3.57, 3.94 (2H,ABq,J=17.4 Hz), 4.34 (3H,s), 5.40 (1H,d,J=4.8 Hz), 5.85 (2H,d,J=55 Hz), 5.93 (1H,d,J=4.8 Hz), 8.34, 8.72 (each 2H,d,J=6.4 Hz), 8.51 (1H,s); IR (KBr, cm^{-1}): 3055, 1781, 1677, 1642, 1523, 1364, 1189, 1071.

WORKING EXAMPLE 4

7β-[2(Z)-Fluoromethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate

The crude lyophilized compound (0.96 g) obtained in Working Example 3 was dissolved in a solution of $NaHCO_3$ (234 mg) in H_2O (15 ml). The solution was subjected to ODS-AM column chromatography (450 ml: eluents=1N HCl 3.06 ml, H_2O 1.0L, 20% aq acetonitrile 0.25L, 30% aq acetonitrile 0.6L). The fractions containing the desired compound were concentrated under reduced pressure, and the concentrate was lyophilized to give the titled compound (600 mg).

Anal Calcd for $C_{21}H_{18}N_8O_8FPS_4.2.0H_2O$: C, 34.81; H, 3.06; N, 15.46; P, 4.27. Found: C, 34.84; H, 3.28; N, 15.43; P, 4.18.

WORKING EXAMPLE 5

7β-[2(Z)-Ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate

Under ice-cooling, 0.6M $NaHCO_3$ (34 ml) was added to a solution of 7β-amino-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate hydrochloride (3.0 g) in a mixture of THF (150 ml) and H_2O (150 ml). To the solution were added portionwise 2-(5-dichlorophosphorylamino-1,2,4-thiadiazol-3-yl)-2(Z)-ethoxyiminoacetyl chloride (4.76 g) and 0.6M $NaHCO_3$ (23 ml) successively. The resulting mixture was stirred at 5° C. for 15 minutes and then at room temperature for 2 hours. Under ice-cooling, the pH of the reaction mixture was adjusted to 5.0 with 1N NaOH, and the mixture was concentrated under reduced pressure. The concentrate was diluted with H_2O (2.5L), and the pH of the solution was adjusted to 3.0with 1N HCl. The mixture was purified by MCI gel SP-207 column chromatography (750 ml: eluents=H_2O 4L, 15% aq EtOH 6L). The fractions containing the desired compound were concentrated under reduced pressure, and the concentrate was lyophilized to give the crude titled compound (2.6 g).

^{1}H NMR (DMSO-d_6) δ: 1.23 (3H,t,J=7 Hz), 3.56, 3.94 (2H,ABq,J=17 Hz), 4.17 (2H,q,J=7 Hz), 4.33 (3H,s), 5.30 (1H,d,J=5 Hz), 5.90 (1H,dd,J=5&8.8 Hz), 8.50, 8.97 (each 2H,d,J=6.4 Hz), 8.98 (1H,s), 9.22 (1H,m), 9.69 (1H,d,J=8.8 Hz).

WORKING EXAMPLE 6

7β-[2(Z)-Ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate

The crude lyophilized compound (1.24 g) obtained in Working Example 5 was dissolved in H_2O (13 ml) containing 1N NaOH (3.24 ml). The solution was subjected to ODS-AM column chromatography (450 ml: eluents=H_2O). The fractions containing sodium salt form of the desired compound were passed through Dowex 50x8 column (H form, 20 to 50 mesh, 100 ml). The eluent was concentrated under reduced pressure, and the concentrate was lyophilized to give the titled compound (377 mg).

Anal Calcd for $C_{22}H_{21}N_8O_8PS_4.3.5H_2O$: C, 35.29; H, 3.77; N, 14.97. Found: C, 35.26; H, 3.45; N, 14.99. ^{1}H NMR (DMSO-d_6) δ: 1.24 (3H,t,J=7 Hz), 3.54, 3.94 (2H,ABq,J=17 Hz), 4.20 (2H,q,J=7 Hz), 4.33 (3H,s), 5.30 (1H,d,J=5.2 Hz), 5.89 (1H,dd,J=5.2&8.6 Hz), 8.51, 8.98 (each 2H,d,J=5.6 Hz), 8.98 (1H,s), 9.17 (1H,m), 9.69 (1H,d,J=8.6 Hz).

WORKING EXAMPLE 7

7β-[2(Z)-Ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate

Trimethylsilylacetamide (919 mg) was added to a suspension of 7β-amino-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem- 4-carboxylate hydrochloride (240 mg) in dichloromethane (4 ml), and the mixture was stirred at room temperature for 40 minutes. To the mixture was added portionwise 2-(5-dichlorophosphorylamino-1,2,4-thiadiazol-3-yl)-2(Z)-ethoxyiminoacetyl chloride (351 mg) under cooling at −15° C., and the mixture was stirred at −15 to −5° C. for 1 hour. After concentration of the reaction mixture under reduced pressure, the concentrate was diluted with H_2O (150 ml). Under ice-cooling, the pH of the mixture was adjusted to 5.0 with 1N NaOH. The mixture was diluted with H_2O (200 ml), and the pH of the mixture was adjusted to 3.0 with 1N HCl. The mixture was purified by MCI gel SP-207 column chromatography (180 ml: eluents=H_2O 0.5L, 15% aq EtOH 0.6L). The fractions containing the desired compound were concentrated under reduced pressure, and the concentrate was lyophilized to give the crude titled compound (100 mg).

^{1}H NMR (DMSO-d_6) δ: 1.23 (3H,t,J=7 Hz), 3.56, 3.94 (2H,ABq,J=17 Hz), 4.17 (2H,q,J=7 Hz), 4.33 (3H,s), 5.30 (1H,d,J=5 Hz), 5.90 (1H,dd,J=5&8.8 Hz), 8.50, 8.97 (each 2H,d,J=6.4 Hz), 8.98 (1H,s), 9.22 (1H,m), 9.69 (1H,d,J=8.8 Hz).

WORKING EXAMPLE 8

The lyophilized 7β-[2(Z)-ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate (300 mg equivalent), obtained in Working Example 6, was dissolved in saline, the pH was adjusted to 6.0, and saline was added to make the total volume 5 ml (60 mg equivalent/ml).

Experiment 1

The lyophilized 7β-[2(Z)-ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate obtained in Working Example 6, was dissolved in mouse plasma to prepare 10 mg equivalent/ml solution. After incubation at 37° C., the transformation rate into 7β-[2(Z)-ethoxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl) acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate (amino form) was measured. The transformation rates in 30 minutes and 1 hour were as follows:

30 minutes 35%

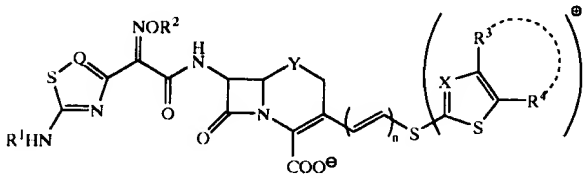
1 hour 62%

INDUSTRIAL APPLICABILITY

The cephem compound (I) has a broad antibacterial spectrum and an excellent antibacterial activity against Gram-negative bacteria and Gram-positive bacteria including *Staphylococcus aureus* and MRSA, and is useful for treatment or prevention of infectious diseases caused by these bacteria. Additionally, the compound (I) has a relatively high solubility in water, and can be advantageously used for injection.

What is claimed is:

1. A compound of the formula:



wherein R^1 is a phosphono group;

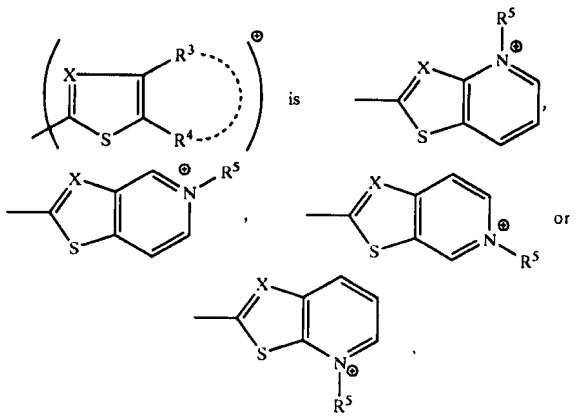
R^2 is a hydrogen atom, an optionally substituted C_{1-6} alkyl group or a C_{3-5} cycloalkyl group;

each of Q and X is a nitrogen atom or CH;

Y is S;

n is 0 or 1;

one of R^3 and R^4 is a pyridinium group which may be substituted and the other is a hydrogen atom or a hydrocarbon group which may be substituted, or R^3 and R^4 taken together may form a quaternized nitrogen-containing heterocyclic ring which may be substituted, wherein when R^3 and R^4 are taken together, the group of the formula



wherein R^5 is an optionally substituted hydrocarbon group; or salt thereof.

2. 7β-[2(Z)-ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazole-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate.

3. A method for producing a pharmaceutical composition comprising

mixing a compound of claim 1 with a pharmaceutically acceptable carrier, diluent or bulking agent.

4. 7β-[2(Z)-ethoxyimino-2-(5-phosphonoamino 1,2,4-thiadiazole-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolythio]-3-cephem-4-carboxylate or its salt.

5. A method for treating a bacterial infection which comprises administering an effective amount of a compound as claimed in claim 1 to a patient suffering from the bacterial infection.

6. A method for treating a bacterial infection which comprises administering an effective amount of a compound as claimed in claim 1 together with at least one of pharmaceutically acceptable carriers, diluents and excipients to a patient suffering from the bacterial infection.

7. A method as claimed in claim 5, wherein the bacterial infection is a MRSA infection.

8. A compound as claimed in claim 1, wherein R^3 is a pyridinium group which may be substituted and R^4 is a hydrogen atom.

9. A compound as claimed in claim 1, wherein Q is a nitrogen atom.

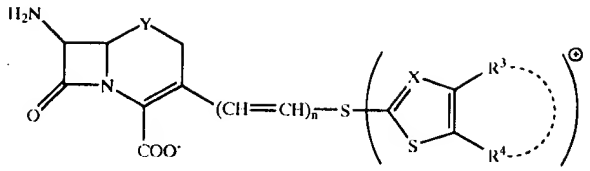
10. A compound as claimed in claim 1, wherein X is a nitrogen atom.

11. A compound as claimed in claim 1, wherein n is 0.

12. A method for treating a bacterial infection which comprises administering an effective amount of a compound as claimed in claim 4 to a patient suffering from the bacterial infection.

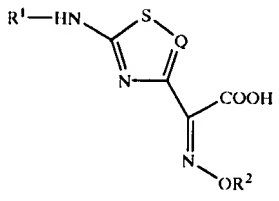
13. A compound as claimed in claim 1, which is 7β-[2(Z)-fluoromethoxyimino-2-(5phophonoamino-1,2,4-thiadiazole-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4carboxylate or its salt.

14. A method for producing a compound as claimed in claim 1, which comprises reacting a compound of the formula:



or its salt;

wherein each symbol has the meaning given in claim 1; with a compound of the formula:



its salt or its reactive derivative;

wherein each symbol has the meaning given in claim 1.

15. A method as claimed in claim 5, wherein the compound is administered by injection.

16. A method for treating a bacterial infection which comprises administering an effective amount of a compound as claimed in claim 4 together with at least one of pharmaceutically acceptable carriers, diluents and excipients to a patient suffering from the bacterial infection.

17. A pharmaceutical composition containing the compound shown in claim 1 and at least one of pharmaceutically acceptable carriers, diluents and bulking agents.

18. A pharmaceutical composition containing the compound of claim 4 and at least one of pharmaceutically acceptable carriers, diluents and bulking agents.

19. A method for producing a pharmaceutical composition comprising mixing a compound of claim 4 with a pharmaceutically acceptable carrier, diluent or bulking agent.

20. A method as claimed in claim 12, wherein the compound is administered by injection.

21. A method as claimed in claim 12, wherein the bacterial infection is a MRSA infection.

* * * * *

EXHIBIT B

US006417175B1

(12) **United States Patent**
Ishikawa et al.

(10) **Patent No.: US 6,417,175 B1**
(45) **Date of Patent: Jul. 9, 2002**

(54) **PHOSPHONOCEPHEM DERIVATIVES, PROCESS FOR THE PREPARATION OF THE SAME, AND USE THEREOF**

(75) Inventors: **Tomoyasu Ishikawa**, Otsu; **Shohei Hashiguchi**, Toyonaka; **Yuji Iizawa**, Muko, all of (JP)

(73) Assignee: **Takeda Chemical Industries, Ltd.**, Osaka (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/555,949**

(22) PCT Filed: **Dec. 17, 1998**

(86) PCT No.: **PCT/JP98/05709**

§ 371 (c)(1),
(2), (4) Date: **Jun. 6, 2000**

(87) PCT Pub. No.: **WO99/32497**

PCT Pub. Date: **Jul. 1, 1999**

(30) **Foreign Application Priority Data**

Dec. 19, 1997 (JP) 9-351499

(51) **Int. Cl.**[7] **C07D 9/6561**; A61K 31/675
(52) **U.S. Cl.** **514/80**; 540/225; 540/227
(58) **Field of Search** 540/227, 225; 514/80

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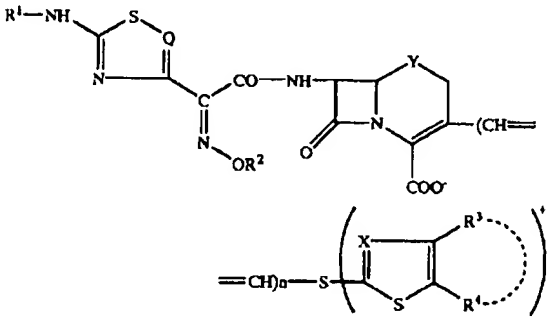
* cited by examiner

Primary Examiner—Mark L. Berch
(74) *Attorney, Agent, or Firm*—Mark Chao; Elaine M. Ramesh

(57) **ABSTRACT**

A novel cephem compound of the formula:



wherein R^1 is a phosphono group or a group convertible to a phosphono group; R^2 is a hydrogen atom or a group having a linkage through a carbon atom; each of Q and X is a nitrogen atom or CH; Y is S, O or CH_2; n is 0 or 1; one of R^3 and R^4 is a pyridinium group which may be substituted and the other is a hydrogen atom or hydrocarbon group which may be substituted, or R^3 and R^4 taken together may form a quaternalized nitrogen-containing heterocyclic ring which may be substituted, or its ester or its salt, which has a superior anti-bacterial activity, stability, absorbability, etc., a production thereof and a pharmaceutical composition containing it, is provided.

21 Claims, No Drawings

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 2

Patent #: 6417175 **Issue Dt:** 07/09/2002 **Application #:** 09555949 **Filing Dt:** 06/06/2000

Inventors: TOMOYASU ISHIKAWA, SHOHEI HASHIGUCHI, YUJI IIZAWA

Title: PHOSPHONOCEPHEM DERIVATIVES, PROCESS FOR THE PREPARATION OF THE SAME, AND USE THEREOF

Assignment: 1

Reel/Frame: 010902/0251 **Recorded:** 06/06/2000 **Pages:** 3

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

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Assignment: 2

Reel/Frame: 015612/0101 **Recorded:** 01/19/2005 **Pages:** 13

Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

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4. Application number(s) or patent number(s): 09555949
Title: Phosphonocephem Derivatives, Their Production and Use
If this document is being filed together with a new application, the execution date of the application is : May 24, 2000
A. Patent Application No.(s)
B. Patent No.(s)
Additional numbers attached? No

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Washington, D.C. 20231

ASSIGNMENT

For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, each undersigned inventor hereby sells and assigns, to TAKEDA CHEMICAL INDUSTRIES LTD., a corporation of Japan, 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan (hereinafter ASSIGNEE) all right, title and interest for the United States, its territories and possessions in and to the following invention and U.S. application filed thereon, and the entire right, title and interest in and to any and all Letters Patents which may be granted therefor in the United States, to be held and enjoyed by said ASSIGNEE, its successors, legal representatives and assigns to the full end of the term or terms for which any and all such Letters Patent may be granted as fully and entirely as would have been held and enjoyed by the undersigned had this Assignment not been made.

Title of Invention : **Phosphonocephem Derivatives, Their Production and Use**

United States Patent Application :

[XX] executed concurrently herewith
[ ] executed on _____
[ ] Serial No. _____ Filed _____

Each of the undersigned acknowledges that this sale and assignment includes any and all divisions or continuations of said United States Patent application, and any and all Letters Patent of the United States which may issue on any such applications, including any and all reissues or extensions thereof.

Each of the undersigned hereby authorizes and requests the Commissioner of Patents and Trademarks to issue any and all such Letters Patent to said ASSIGNEE, its successors or assigns in accordance herewith;

Each of the undersigned warrants and covenants that he has the full and unencumbered right to sell and assign the interests herein sold and assigned and that he has not executed and will not execute any document or instrument in conflict herewith;

Each of the undersigned further covenants and agrees he will communicate to said ASSIGNEE, its successors, legal representatives or assigns all information known to him relating to said invention or patent application and that he will execute and deliver any papers, make all rightful oaths, assist in and testify in any related proceedings including interferences or lawsuits concerning this application or continuation, division or reissue thereof, and perform all other lawful acts deemed necessary or desirable by said ASSIGNEE, its successors, legal representatives or assigns to obtain a grant of a valid United States Patent on said invention;

Each of the undersigned hereby grants ASSIGNEE and its legal representatives, the power to insert in this Assignment any further identification which may be necessary or desirable to comply with the rules of the U.S. Patent and Trademark Office for recordation of this Assignment and specifically, the power to insert in the space provided above, the filing date and application number of the application when known.

In witness hereof, executed by the undersigned on the date(s) opposite the undersigned names.

NAMES AND SIGNATURES OF INVENTORS		
1.Name: Tomoyasu ISHIKAWA	Signature: Tomoyasu Ishikawa	Date: May 24, 2000
2.Name: Shohei HASHIGUCHI	Signature: Shohei Hashiguchi	Date: May 24 2000
3.Name: Yuji IIZAWA	Signature: Yuji Iizawa	Date: May 24 2000
4.Name:	Signature:	Date:
5.Name:	Signature:	Date:
6.Name:	Signature:	Date:
NAMES AND SIGNATURES OF WITNESSES*		
Name/ Norikazu Tamura For: 1, 2, 3	Signature: Norikazu Tamura	Date: May 24, 2000
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Name/ For:	Signature:	Date:
Name/ For:	Signature:	Date:
Name/ For:	Signature:	Date:
Name/ For:	Signature:	Date:

*Notice for Witnesses! Please indicate which inventor(s) you are signing for by writing the corresponding numbers after "For:"

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	CHANGE OF NAME

CONVEYING PARTY DATA

Name	Execution Date
Takeda Chemical Industries, Ltd.	06/29/2004

RECEIVING PARTY DATA

Name:	Takeda Pharmaceutical Company, Limited
Street Address:	1-1, Doshomachi 4-chome
City:	Chuo-ku, Osaka
State/Country:	JAPAN

PROPERTY NUMBERS Total: 356

Property Type	Number
Patent Number:	4612364
Patent Number:	4677191
Patent Number:	4683288
Patent Number:	4689333
Patent Number:	4777294
Patent Number:	4799449
Patent Number:	4803303
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Patent Number:	6756472
Patent Number:	RE36575

CORRESPONDENCE DATA

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Address Line 2: Suite 800

Address Line 4: Washington, DISTRICT OF COLUMBIA 20037

NAME OF SUBMITTER:	David J. Cushing

Total Attachments: 1
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THE OSAKA CHAMBER OF COMMERCE & INDUSTRY

2-8 HOMMACHIBASHI, CHUO-KU, OSAKA 540-0029, JAPAN.
FAX : (06)6944-6248 TEL : (06)6944-6411
URL : http://www.osaka.cci.or.jp/

September 13, 2004

To whom it may concern:

CERTIFICATE OF MEMBERSHIP

This is to certify that the undermentioned company is registered as a member of this Chamber.

Company name: Takeda Pharmaceutical Company Limited

(The former company name in English was Takeda Chemical Industries, Ltd. until June 29, 2004.)

Address: 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan

Membership Number: KT-01-00080

The Osaka Chamber of Commerce & Industry

Yoshinobu Kobayashi
Authorized Signatory

EXHIBIT C

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner:	Tomoyasu ISHIKAWA et al.		
Application No.:	09/555,949	Filed:	12/17/1998
Patent No.:	6,417,175	Issue Date:	7/9/2002
Docket Number:	087147-0640		
Entitled:	PHOSPHONOCEPHEM DERIVATIVES, PROCESS FOR THE PREPARATION OF THE SAME, AND USE THEREOF		

Takeda Pharmaceutical Company Limited
(Name of Assignee)

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☒ the assignee of the entire right, title, and interest; or
2. ☐ an assignee of less than the entire right, title, and interest
   The extent (by percentage) of its ownership interest is %

in the patent application/patent identified above by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel/Frame or for which a copy thereof is attached.

OR

B. ☒ A chain of title from the inventors of the patent application identified above, to the current assignee as shown below:

1. From: Tomoyasu ISHIKAWA; Shohei HASHIGUCHI; and Yuji IIZAWA To: Takeda Chemical Industries Ltd.
   The document was recorded in the United States Patent and Trademark Office at
   Reel 010902, Frame 0251.

2. From: Takeda Chemical Industries, Ltd. To: Takeda Pharmaceutical Company Limited
   The document was recorded in the United States Patent and Trademark Office at
   Reel 015612, Frame 0101.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☐ Copies of assignments or other documents in the chain of title are attached.

[**NOTE**: A separate copy (i.e., a true copy of the original document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Stephen B. Maebius/	Dec. 12, 2010
Signature	Date
Stephen B. Maebius	(202) 672-5569
Printed or Typed Name	Telephone Number
Attorney	
Title	

PTO/SB/80 (01-06)
Approved for use through 12/31/2008. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

☒ Practitioners associated with the Customer Number: 22428

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

☒ The address associated with Customer Number: 22428

OR

☐ Firm or Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

Assignee Name and Address:

Takeda Pharmaceutical Company, Limited

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	X	Date	August 28, 2006
Name	Hiroshi AKIMOTO, Ph.D.	Telephone	
Title	Managing Director, Member of the Board.		

EXHIBIT D

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Teflaro safely and effectively. See full prescribing information for Teflaro™.

Teflaro™ (ceftaroline fosamil) injection for intravenous (IV) use

Initial U.S. Approval: 2011

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Teflaro and other antibacterial drugs, Teflaro should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

----------INDICATIONS AND USAGE----------

Teflaro™ is a cephalosporin antibacterial indicated for the treatment of the following infections caused by designated susceptible bacteria:

- Acute bacterial skin and skin structure infections (ABSSSI) (1.1)
- Community-acquired bacterial pneumonia (CABP) (1.2)

----------DOSAGE AND ADMINISTRATION----------

- 600 mg every 12 hours by IV infusion administered over 1 hour in adults ≥ 18 years of age (2.1)
- Dosage adjustment in patients with renal impairment (2.2)

Estimated Creatinine Clearance# (mL/min)	Teflaro Dosage Regimen
> 50	No dosage adjustment necessary
> 30 to ≤ 50	400 mg IV (over 1 hour) every 12 hours
≥ 15 to ≤ 30	300 mg IV (over 1 hour) every 12 hours
End-stage renal disease (ESRD), including hemodialysis	200 mg IV (over 1 hour) every 12 hours

As calculated using the Cockcroft-Gault formula

----------DOSAGE FORMS AND STRENGTHS ----------

600 mg or 400 mg of sterile Teflaro powder in single-use 20 mL vials. (3)

----------CONTRAINDICATIONS----------

Known serious hypersensitivity to ceftaroline or other members of the cephalosporin class. (4)

----------WARNINGS AND PRECAUTIONS----------

- Serious hypersensitivity (anaphylactic) reactions have been reported with beta-lactam antibiotics, including ceftaroline. Exercise caution in patients with known hypersensitivity to beta-lactam antibiotics. (5.1)
- *Clostridium difficile*-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agents, including Teflaro. Evaluate if diarrhea occurs. (5.2)
- Direct Coombs' test seroconversion has been reported with Teflaro. If anemia develops during or after therapy, a diagnostic workup for drug-induced hemolytic anemia should be performed and consideration given to discontinuation of Teflaro. (5.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions occurring in >2 % of patients are diarrhea, nausea, and rash. (6.3)

To report SUSPECTED ADVERSE REACTIONS, contact Forest Pharmaceuticals, Inc., at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

Dosage adjustment is required in patients with moderate or severe renal impairment and in ESRD patients, including patients on hemodialysis. (2.2, 12.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: XX/20XX

FULL PRESCRIBING INFORMATION: CONTENTS*

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1.2 Community-Acquired Bacterial Pneumonia
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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. Indications and Usage

Teflaro™ (ceftaroline fosamil) is indicated for the treatment of patients with the following infections caused by susceptible isolates of the designated microorganisms.

1.1 Acute Bacterial Skin and Skin Structure Infections

Teflaro is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae, and Klebsiella oxytoca.*

1.2 Community-Acquired Bacterial Pneumonia

Teflaro is indicated for the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae, Klebsiella pneumoniae, Klebsiella oxytoca,* and *Escherichia coli.*

1.3 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Teflaro and other antibacterial drugs, Teflaro should be used to treat only ABSSSI or CABP that are proven or strongly suspected to be caused by susceptible bacteria. Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to ceftaroline. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2. Dosage and Administration

2.1 Recommended Dosage

The recommended dosage of Teflaro is 600 mg administered every 12 hours by intravenous (IV) infusion over 1 hour in patients ≥ 18 years of age. The duration of therapy should be guided by the severity and site of infection and the patient's clinical and bacteriological progress.

The recommended dosage and administration by infection is described in Table 1.

Table 1: Dosage of Teflaro by Infection

Infection	Dosage	Frequency	Infusion Time (hours)	Recommended Duration of Total Antimicrobial Treatment
Acute Bacterial Skin and Skin Structure Infection (ABSSSI)	600 mg	Every 12 hours	1	5-14 days
Community-Acquired Bacterial Pneumonia (CABP)	600 mg	Every 12 hours	1	5-7 days

2.2 Patients with Renal Impairment

Table 2: Dosage of Teflaro in Patients with Renal Impairment

Estimated CrCl[a] (mL/min)	Recommended Dosage Regimen for Teflaro
> 50	No dosage adjustment necessary
> 30 to ≤ 50	400 mg IV (over 1 hour) every 12 hours
≥ 15 to ≤ 30	300 mg IV (over 1 hour) every 12 hours
End-stage renal disease, including hemodialysis[b]	200 mg IV (over 1 hour) every 12 hours[c]

[a] Creatinine clearance (CrCl) estimated using the Cockcroft-Gault formula.

[b] End-stage renal disease is defined as CrCl < 15 mL/min.

[c] Teflaro is hemodialyzable; thus Teflaro should be administered after hemodialysis on hemodialysis days.

2.3 Preparation of Solutions

Aseptic technique must be followed in preparing the infusion solution. The contents of Teflaro vial should be constituted with 20 mL Sterile Water for Injection, USP. The preparation of Teflaro solutions is summarized in Table 3.

Table 3: Preparation of Teflaro for Intravenous Use

Dosage Strength (mg)	Volume of Diluent To Be Added (mL)	Approximate Ceftaroline fosamil Concentration (mg/mL)	Amount to Be Withdrawn
400	20	20	Total Volume
600	20	30	Total Volume

The constituted solution must be further diluted in ≥ 250 mL before infusion. Appropriate infusion solutions include: 0.9% Sodium Chloride Injection, USP (normal saline); 5% Dextrose Injection, USP; 2.5% Dextrose Injection, USP, and 0.45% Sodium Chloride Injection, USP; or Lactated Ringer's Injection, USP. The resulting solution should be administered over approximately 1 hour.

Constitution time is less than 2 minutes. Mix gently to constitute and check to see that the contents have dissolved completely. Parenteral drug products should be inspected visually for particulate matter prior to administration.

The color of Teflaro infusion solutions ranges from clear, light to dark yellow depending on the concentration and storage conditions. When stored as recommended, the product potency is not affected.

Studies have shown that the constituted solution in the infusion bag should be used within 6 hours when stored at room temperature or within 24 hours when stored under refrigeration at 2 to 8° C (36 to 46° F).

The compatibility of Teflaro with other drugs has not been established. Teflaro should not be mixed with or physically added to solutions containing other drugs.

3. Dosage Forms and Strengths

Teflaro is supplied in single-use, clear glass vials containing either 600 mg or 400 mg of sterile ceftaroline fosamil powder.

4. Contraindications

Teflaro is contraindicated in patients with known serious hypersensitivity to ceftaroline or other members of the cephalosporin class. Anaphylaxis and anaphylactoid reactions have been reported with ceftaroline.

5. Warnings and Precautions

5.1 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterials. Before therapy with Teflaro is instituted, careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or carbapenems should be made. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross sensitivity among beta-lactam antibacterial agents has been clearly established.

If an allergic reaction to Teflaro occurs, the drug should be discontinued. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures, that may include airway management, oxygen, intravenous fluids, antihistamines, corticosteroids, and vasopressors as clinically indicated.

5.2 *Clostridium difficile*-associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including Teflaro, and may range in severity from mild diarrhea to fatal colitis.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, antibacterials not directed against *C. difficile* should be discontinued, if possible. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated *[see Adverse Reactions (6.3)]*.

5.3 Direct Coombs Test Seroconversion

Seroconversion from a negative to a positive direct Coombs' test result occurred in 120/1114 (10.8%) of patients receiving Teflaro and 49/1116 (4.4%) of patients receiving comparator drugs in the four pooled Phase 3 trials.

In the pooled Phase 3 CABP trials, 51/520 (9.8%) of Teflaro-treated patients compared to 24/534 (4.5%) of ceftriaxone-treated patients seroconverted from a negative to a positive direct Coombs' test result. No adverse reactions representing hemolytic anemia were reported in any treatment group.

If anemia develops during or after treatment with Teflaro, drug-induced hemolytic anemia should be considered. Diagnostic studies including a direct Coombs' test, should be performed. If drug-induced hemolytic anemia is suspected, discontinuation of Teflaro should be considered and supportive care should be administered to the patient (i.e. transfusion) if clinically indicated.

5.4 Development of Drug-Resistant Bacteria

Prescribing Teflaro in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6. Adverse Reactions

The following serious events are described in greater detail in the Warnings and Precautions section

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- *Clostridium difficile*-associated diarrhea *[see Warnings and Precautions (5.2)]*
- Direct Coombs' test seroconversion *[see Warnings and Precautions (5.3)]*

6.1 Adverse Reactions from Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be compared directly to rates from clinical trials of another drug and may not reflect rates observed in practice.

Teflaro was evaluated in four controlled comparative Phase 3 clinical trials (two in ABSSSI and two in CABP) which included 1300 adult patients treated with Teflaro (600 mg administered by IV over 1 hour every 12h) and 1297 patients treated with comparator (vancomycin plus aztreonam or ceftriaxone) for a treatment period up to 21 days. The median age of patients treated with Teflaro was 54 years, ranging between 18 and 99 years old. Patients treated with Teflaro were predominantly male (63%) and Caucasian (82%).

6.2 Serious Adverse Events and Adverse Events Leading to Discontinuation

In the four pooled Phase 3 clinical trials, serious adverse events occurred in 98/1300 (7.5%) of patients receiving Teflaro and 100/1297 (7.7%) of patients receiving comparator drugs. The most common SAEs in both the Teflaro and comparator treatment groups were in the respiratory and infection system organ classes (SOC). Treatment discontinuation due to adverse events occurred in 35/1300 (2.7%) of patients receiving Teflaro and 48/1297 (3.7%) of patients receiving comparator drugs with the most common adverse events leading to discontinuation being hypersensitivity for both treatment groups at a rate of 0.3% in the Teflaro group and 0.5% in comparator group.

6.3 Most Common Adverse Reactions

No adverse reactions occurred in greater than 5% of patients receiving Teflaro. The most common adverse reactions occurring in > 2% of patients receiving Teflaro in the pooled phase 3 clinical trials were diarrhea, nausea, and rash.

Table 4 lists adverse reactions occurring in ≥ 2% of patients receiving Teflaro in the pooled Phase 3 clinical trials.

Table 4: Adverse Reactions Occurring in ≥ 2% of Patients Receiving Teflaro in the Phase 3 Clinical Trials

System Organ Class/ Preferred Term	Pooled Phase 3 Clinical Trials (four trials, two in ABSSSI and two in CABP)	
	Teflaro (N=1300)	Pooled Comparators[a] (N=1297)
Gastrointestinal disorders		
Diarrhea	5 %	3 %
Nausea	4 %	4 %
Constipation	2 %	2 %
Vomiting	2 %	2 %
Investigations		
Increased transaminases	2%	3 %
Metabolism and nutrition disorders		
Hypokalemia	2 %	3 %
Skin and subcutaneous tissue disorders		
Rash	3%	2%
Vascular disorders		
Phlebitis	2%	1%

[a] Comparators included vancomycin 1 gram IV every 12h plus aztreonam 1 gram IV every 12h in the Phase 3 ABSSSI trials, and ceftriaxone 1 gram IV every 24h in the Phase 3 CABP trials.

6.4 Other Adverse Reactions Observed During Clinical Trials of Teflaro

Following is a list of additional adverse reactions reported by the 1740 patients who received Teflaro in any clinical trial with incidences less than 2%. Events are categorized by System Organ Class.

Blood and lymphatic system disorders - Anemia, Eosinophilia, Neutropenia, Thrombocytopenia

Cardiac disorders - Bradycardia, Palpitations

Gastrointestinal disorders - Abdominal pain

General disorders and administration site conditions - Pyrexia

Hepatobiliary disorders - Hepatitis

Immune system disorders - Hypersensitivity, Anaphylaxis

Infections and infestations - *Clostridium difficile* colitis

Metabolism and nutrition disorders - Hyperglycemia, Hyperkalemia

Nervous system disorders - Dizziness, Convulsion

Renal and urinary disorders - Renal failure

Skin and subcutaneous tissue disorders - Urticaria

7. Drug Interactions

No clinical drug-drug interaction studies have been conducted with Teflaro. There is minimal potential for drug-drug interactions between Teflaro and CYP450 substrates, inhibitors, or inducers; drugs known to undergo active renal secretion; and drugs that may alter renal blood flow *[see Clinical Pharmacology (12.3)]*.

8. Use in Specific Populations

8.1 Pregnancy

Category B

Developmental toxicity studies performed with ceftaroline fosamil in rats at IV doses up to 300 mg/kg demonstrated no maternal toxicity and no effects on the fetus. A separate toxicokinetic study showed that ceftaroline exposure in rats (based on AUC) at this dose level was approximately 8 times the exposure in humans given 600 mg every 12 hours. There were no drug-induced malformations in the offspring of rabbits given IV doses of 25, 50, and 100 mg/kg, despite maternal toxicity. Signs of maternal toxicity appeared secondary to the sensitivity of the rabbit gastrointestinal system to broad-spectrum antibacterials and included changes in fecal output in all groups and dose-related reductions in body weight gain and food consumption at ≥ 50 mg/kg; these were associated with an increase in spontaneous abortion at 50 and 100 mg/kg. The highest dose was also associated with maternal moribundity and mortality. An increased incidence of a common rabbit skeletal variation, angulated hyoid alae, was also observed at the maternally toxic doses of 50 and 100 mg/kg. A separate toxicokinetic study showed that ceftaroline exposure in rabbits (based on AUC) was approximately 0.8 times the exposure in humans given 600 mg every 12 hours at 25 mg/kg and 1.5 times the human exposure at 50 mg/kg.

Ceftaroline fosamil did not affect the postnatal development or reproductive performance of the offspring of rats given IV doses up to 450 mg/kg/day. Results from a toxicokinetic study conducted in pregnant rats with doses up to 300 mg/kg suggest that exposure was ≥ 8 times the exposure in humans given 600 mg every 12 hours.

There are no adequate and well-controlled trials in pregnant women. Teflaro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether ceftaroline is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Teflaro is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1300 patients treated with Teflaro in the Phase 3 ABSSSI and CABP trials, 397 (30.5%) were ≥ 65 years of age. The clinical cure rates in the Teflaro group (Clinically Evaluable [CE] Population) were similar in patients ≥ 65 years of age compared with patients < 65 years of age in both the ABSSSI and CABP trials.

The adverse event profiles in patients ≥ 65 years of age and in patients < 65 years of age were similar. The percentage of patients in the Teflaro group who had at least one adverse event was 52.4% in patients ≥ 65 years of age and 42.8% in patients < 65 years of age for the two indications combined.

Ceftaroline is excreted primarily by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this age group and it may be useful to monitor renal function. Elderly subjects had greater ceftaroline exposure relative to non-elderly subjects when administered the same single dose of Teflaro. However, higher exposure in elderly subjects was mainly attributed to age-related changes in renal function. Dosage adjustment for elderly patients should be based on renal function *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8.6 Patients with Renal Impairment

Dosage adjustment is required in patients with moderate (CrCl > 30 to ≤ 50 mL/min) or severe (CrCl ≥ 15 to ≤ 30 mL/min) renal impairment and in patients with end-stage renal disease (ESRD – defined as CrCl < 15 mL/min), including patients on hemodialysis (HD)*[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

10. Overdosage

In the event of overdose, Teflaro should be discontinued and general supportive treatment given.

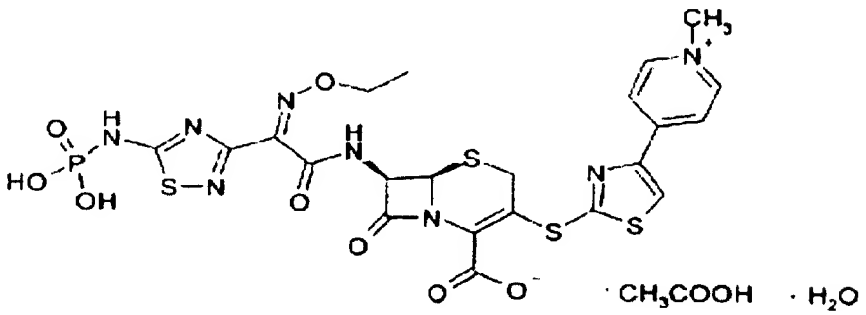
Ceftaroline can be removed by hemodialysis. In subjects with ESRD administered 400 mg of Teflaro, the mean total recovery of ceftaroline in the dialysate following a 4-hour hemodialysis session started 4 hours after dosing was 76.5 mg (21.6% of the dose). However, no information is available on the use of hemodialysis to treat overdosage *[see Clinical Pharmacology (12.3)]*.

11. Description

Teflaro is a sterile, semi-synthetic, broad-spectrum, prodrug antibacterial of cephalosporin class of beta-lactams (β-lactams). Chemically, the prodrug, ceftaroline fosamil monoacetate monohydrate is (6*R*,7*R*)-7-{(2*Z*)-2-(ethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido}-3-{[4-(1-methylpyridin-1-ium-4-yl)-1,3-thiazol-2-

yl]sulfanyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate monoacetate monohydrate. Its molecular weight is 762.75. The empirical formula is $C_{22}H_{21}N_8O_8PS_4.C_2H_4O_2.H_2O$.

Figure 1: Chemical structure of ceftaroline fosamil



Teflaro vials contain either 600 mg or 400 mg of anhydrous ceftaroline fosamil. The powder for injection is formulated from ceftaroline fosamil monoacetate monohydrate, a pale yellowish-white to light yellow sterile powder. All references to ceftaroline activity are expressed in terms of the prodrug, ceftaroline fosamil. The powder is constituted for IV injection *[see Dosage and Administration (2.3)]*.

Each vial of Teflaro contains ceftaroline fosamil and L-arginine, which results in a constituted solution at pH 4.8 to 6.5.

12. Clinical Pharmacology

Ceftaroline fosamil is the water-soluble prodrug of the bioactive ceftaroline *[see Clinical Pharmacology (12.3)]*.

12.1 Mechanism of Action

Ceftaroline is an antibacterial drug *[see Clinical Pharmacology (12.4)]*.

12.2 Pharmacodynamics

As with other beta-lactam antimicrobial agents, the time that unbound plasma concentration of ceftaroline exceeds the minimum inhibitory concentration (MIC) of the infecting organism has been shown to best correlate with efficacy in a neutropenic murine thigh infection model with *S. aureus* and *S. pneumoniae*.

Exposure-response analysis of Phase 2/3 ABSSSI trials supports the recommended dosage regimen of Teflaro 600 mg every 12 hours by IV infusion over 1 hour. For Phase 3 CABP trials, an exposure-response relationship could not be identified due to the limited range of ceftaroline exposures in the majority of patients.

Cardiac Electrophysiology

In a randomized, positive- and placebo-controlled crossover thorough QTc study, 54 healthy subjects were each administered a single dose of Teflaro 1500 mg, placebo, and a positive control by IV infusion over 1 hour. At the 1500 mg dose of Teflaro, no significant effect on QTc interval was detected at peak plasma concentration or at any other time.

12.3 Pharmacokinetics

The mean pharmacokinetic parameters of ceftaroline in healthy adults (n=6) with normal renal function after single and multiple 1-hour IV infusions of 600 mg ceftaroline fosamil administered every 12 hours are summarized in Table 5. Pharmacokinetic parameters were similar for single and multiple dose administration.

Table 5: Mean (Standard Deviation) Pharmacokinetic Parameters of Ceftaroline IV in Healthy Adults

Parameter	Single 600 mg Dose Administered as a 1-Hour Infusion (n=6)	Multiple 600 mg Doses Administered Every 12 Hours as 1-Hour Infusions for 14 Days

		(n=6)
C_{max} (mcg/mL)	19.0 (0.71)	21.3 (4.10)
T_{max} (h)[a]	1.00 (0.92-1.25)	0.92 (0.92-1.08)
AUC (mcg•h/mL) [b]	56.8 (9.31)	56.3 (8.90)
$T_{1/2}$ (h)	1.60 (0.38)	2.66 (0.40)
CL (L/h)	9.58 (1.85)	9.60 (1.40)

[a] Reported as median (range)

[b] $AUC_{0-\infty}$ for single-dose administration, AUC_{0-tau} for multiple-dose administration, C_{max}, maximum observed concentration; T_{max}, time of C_{max}; $AUC_{0-\infty}$, area under concentration-time curve from time 0 to infinity; AUC_{0-tau}, area under concentration-time curve over dosing interval (0-12 hours); $T_{1/2}$, terminal elimination half-life; CL, plasma clearance

The C_{max} and AUC of ceftaroline increase approximately in proportion to dose within the single dose range of 50 to 1000 mg. No appreciable accumulation of ceftaroline is observed following multiple IV infusions of 600 mg administered every 12 hours for up to 14 days in healthy adults with normal renal function.

Distribution

The average binding of ceftaroline to human plasma proteins is approximately 20% and decreases slightly with increasing concentrations over 1-50 mcg/mL (14.5-28.0%). The median (range) steady-state volume of distribution of ceftaroline in healthy adult males (n=6) following a single 600 mg IV dose of radiolabeled ceftaroline fosamil was 20.3 L (18.3-21.6 L), similar to extracellular fluid volume.

Metabolism

Ceftaroline fosamil is converted into bioactive ceftaroline in plasma by a phosphatase enzyme and concentrations of the prodrug are measurable in plasma primarily during IV infusion. Hydrolysis of the beta-lactam ring of ceftaroline occurs to form the microbiologically inactive, open-ring metabolite ceftaroline M-1. The mean (SD) plasma ceftaroline M-1 to ceftaroline $AUC_{0-\infty}$ ratio following a single 600 mg IV infusion of ceftaroline fosamil in healthy adults (n=6) with normal renal function is 28% (3.1%).

When incubated with pooled human liver microsomes, ceftaroline was metabolically stable (< 12% metabolic turnover), indicating that ceftaroline is not a substrate for hepatic CYP450 enzymes.

Excretion

Ceftaroline and its metabolites are primarily eliminated by the kidneys. Following administration of a single 600 mg IV dose of radiolabeled ceftaroline fosamil to healthy male adults (n=6), approximately 88% of radioactivity was recovered in urine and 6% in feces within 48 hours. Of the radioactivity recovered in urine approximately 64% was excreted as ceftaroline and approximately 2% as ceftaroline M-1. The mean (SD) renal clearance of ceftaroline was 5.56 (0.20) L/h, suggesting that ceftaroline is predominantly eliminated by glomerular filtration.

Specific Populations

Renal Impairment

Following administration of a single 600 mg IV dose of Teflaro, the geometric mean $AUC_{0-\infty}$ of ceftaroline in subjects with mild (CrCl > 50 to ≤ 80 mL/min, n=6) or moderate (CrCl > 30 to ≤ 50 mL/min, n=6) renal impairment was 19% and 52% higher, respectively, compared to healthy subjects with normal renal function (CrCl > 80 mL/min, n=6). Following administration of a single 400 mg IV dose of Teflaro, the geometric mean $AUC_{0-\infty}$ of ceftaroline in subjects with severe (CrCl ≥ 15 to ≤30 mL/min, n=6) renal impairment was 115% higher compared to healthy subjects with normal renal function (CrCl > 80 mL/min, n=6). Dosage adjustment is recommended in patients with moderate and severe renal impairment *[see Dosage and Administration (2.2)]*.

A single 400 mg dose of Teflaro was administered to subjects with ESRD (n=6) either 4 hours prior to or 1 hour after hemodialysis (HD). The geometric mean ceftaroline AUC0-∞ following the post-HD infusion was 167% higher compared to healthy subjects with normal renal function (CrCl > 80 mL/min, n=6). The mean recovery of ceftaroline in

the dialysate following a 4-hour HD session was 76.5 mg, or 21.6% of the administered dose. Dosage adjustment is recommended in patients with ESRD (defined as CrCL < 15 mL/min), including patients on HD [see Dosage and Administration (2.2)].

Hepatic Impairment

The pharmacokinetics of ceftaroline in patients with hepatic impairment have not been established. As ceftaroline does not appear to undergo significant hepatic metabolism, the systemic clearance of ceftaroline is not expected to be significantly affected by hepatic impairment.

Geriatric Patients

Following administration of a single 600 mg IV dose of Teflaro to healthy elderly subjects (≥ 65 years of age, n=16), the geometric mean AUC0-∞ of ceftaroline was ~33% higher compared to healthy young adult subjects (18-45 years of age, n=16). The difference in AUC0-∞ was mainly attributable to age-related changes in renal function. Dosage adjustment for Teflaro in elderly patients should be based on renal function [see Dosage and Administration (2.2)].

Pediatric Patients

The pharmacokinetics of ceftaroline were evaluated in adolescent patients (ages 12 to 17, n=7) with normal renal function following administration of a single 8 mg/kg IV dose of Teflaro (or 600 mg for subjects weighing > 75 kg). The mean plasma clearance and terminal phase volume of distribution for ceftaroline in adolescent subjects were similar to healthy adults (n=6) in a separate study following administration of a single 600 mg IV dose. However, the mean C_{max} and $AUC_{0-\infty}$ for ceftaroline in adolescent subjects who received a single 8 mg/kg dose were 10% and 23% less than in healthy adult subjects who received a single 600 mg IV dose.

Gender

Following administration of a single 600 mg IV dose of Teflaro to healthy elderly males (n=10) and females (n=6) and healthy young adult males (n=6) and females (n=10), the mean C_{max} and $AUC_{0-\infty}$ for ceftaroline were similar between males and females, although there was a trend for higher C_{max} (17%) and $AUC_{0-\infty}$ (6-15%) in female subjects. Population pharmacokinetic analysis did not identify any significant differences in ceftaroline AUC_{0-tau} based on gender in Phase 2/3 patients with ABSSSI or CABP. No dose adjustment is recommended based on gender.

Race

A population pharmacokinetic analysis was performed to evaluate the impact of race on the pharmacokinetics of ceftaroline using data from Phase 2/3 ABSSSI and CABP trials. No significant differences in ceftaroline AUC_{0-tau} was observed across White (n=35), Hispanic (n=34), and Black (n=17) race groups for ABSSSI patients. Patients enrolled in CABP trials were predominantly categorized as White (n=115); thus there were too few patients of other races to draw any conclusions. No dosage adjustment is recommended based on race.

Drug Interactions

In vitro studies in human liver microsomes indicate that ceftaroline does not inhibit the major cytochrome P450 isoenzymes CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. In vitro studies in human hepatocytes also demonstrate that ceftaroline and its inactive open-ring metabolite are not inducers of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5. Therefore Teflaro is not expected to inhibit or induce the clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner.

Population pharmacokinetic analysis did not identify any clinically relevant differences in ceftaroline exposure (C_{max} and AUC_{0-tau}) in Phase 2/3 patients with ABSSSI or CABP who were taking concomitant medications that are known inhibitors, inducers, or substrates of the cytochrome P450 system; anionic or cationic drugs known to undergo active renal secretion; and vasodilator or vasoconstrictor drugs that may alter renal blood flow.

12.4 Microbiology

Mode of Action

Ceftaroline is a cephalosporin with in vitro activity against Gram-positive and -negative bacteria. The bactericidal action of ceftaroline is mediated through binding to essential penicillin-binding proteins (PBPs). Ceftaroline is bactericidal against *S. aureus* due to its affinity for PBP2a and against *Streptococcus pneumoniae* due to its affinity for PBP2x.

Mechanisms of Resistance

Ceftaroline is not active against Gram-negative bacteria producing extended spectrum beta-lactamases (ESBLs) from the TEM, SHV or CTX-M families, serine carbapenemases (such as KPC), class B metallo-beta-lactamases, or class C (AmpC cephalosporinases).

Cross-Resistance

Although cross-resistance may occur, some isolates resistant to other cephalosporins may be susceptible to ceftaroline.

Interaction with Other Antimicrobials

In vitro studies have not demonstrated any antagonism between ceftaroline or other commonly used antibacterial agents (e.g., vancomycin, linezolid, daptomycin, levofloxacin, azithromycin, amikacin, aztreonam, tigecycline, and meropenem).

Ceftaroline has been shown to be active against most of the following bacteria, both in vitro and in clinical infections *[see Indications and Usage (1)]*.

Skin Infections

Gram-positive bacteria
Staphylococcus aureus (including methicillin-susceptible and -resistant isolates)
Streptococcus pyogenes
Streptococcus agalactiae

Gram-negative bacteria
Escherichia coli
Klebsiella pneumoniae
Klebsiella oxytoca

Community-Acquired Bacterial Pneumonia (CABP)

Gram-positive bacteria
Streptococcus pneumoniae
Staphylococcus aureus (methicillin-susceptible isolates only)

Gram-negative bacteria
Haemophilus influenzae
Klebsiella pneumoniae
Klebsiella oxytoca
Escherichia coli

The following in vitro data are available, but their clinical significance is unknown. Ceftaroline exhibits in vitro MICs of 1 mcg/mL or less against most (≥ 90%) isolates of the following bacteria; however, the safety and effectiveness of Teflaro in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Gram-positive bacteria
Streptococcus dysgalactiae

Gram-negative bacteria
Citrobacter koseri
Citrobacter freundii
Enterobacter cloacae
Enterobacter aerogenes
Moraxella catarrhalis
Morganella morganii
Proteus mirabilis
Haemophilus parainfluenzae

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method[1,3], (broth, and/or agar). Broth dilution MICs need to be read within 18 hours due to degradation of ceftaroline activity by 24 hours. The MIC values should be interpreted according to the criteria in Table 6.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized method. This procedure uses paper disks impregnated with 30 mcg of ceftaroline to test the susceptibility of bacteria to ceftaroline. The disk diffusion interpretive criteria are provided in Table 6.

Table 6: Susceptibility Interpretive Criteria for Ceftaroline

Pathogen and Isolate Source	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
Staphylococcus aureus (includes methicillin-resistant isolates - skin isolates only) - See **NOTE** below	≤1[a]	—	—	≥24	—	—
Streptococcus agalactiae[a] *(skin isolates only)*	≤0.03	—	—	≥26	—	—
Streptococcus pyogenes[a] (skin isolates only)	≤0.015	—	—	≥24	—	—
Streptococcus pneumoniae[a] (CABP isolates only)	≤ 0.25	—	—	≥27	—	—
Haemophilus influenzae (CABP isolates only)	≤0.12	—	—	≥33	—	—
Enterobacteriaceae[b] (CABP and skin isolates)	≤ 0.5	1	≥2	≥23	20-22	≤19

S = susceptible, I = intermediate, R = resistant

NOTE: Clinical efficacy of Teflaro to treat lower respiratory infections such as community-acquired bacterial pneumonia due to MRSA has not been studied in adequate and well controlled trials (See "Clinical Trials" section 14)

[a] The current absence of resistant isolates precludes defining any results other than "Susceptible."Isolates yielding MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.

[b] Clinical efficacy was shown for the following *Enterobacteriaceae: Escherichia coli, Klebsiella pneumoniae, and Klebsiella oxytoca.*

A report of "Susceptible" indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentration at the infection site necessary to inhibit growth of the pathogen. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.[1, 2, 3] Standard ceftaroline powder should provide the following range of MIC values provided in Table 7. For the diffusion technique using the 30-mcg ceftaroline disk the criteria provided in Table 7 should be achieved.

Table 7: Acceptable Quality Control Ranges for Susceptibility Testing

Quality Control Organism	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
Staphylococcus aureus ATCC 25923	Not Applicable	26 - 35
Staphylococcus aureus ATCC 22913	0.12 - 0.5	Not Applicable
Escherichia coli ATCC 25922	0.03 - 0.12	26 - 34
Haemophilus influenzae ATCC 49247	0.03 - 0.12	29 - 39
Streptococcus pneumoniae ATCC 49619	0.008 - 0.03	31 - 41

ATCC = American Type Culture Collection

13. Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies have not been conducted with ceftaroline.

Ceftaroline fosamil did not show evidence of mutagenic activity in in vitro tests that included a bacterial reverse mutation assay and the mouse lymphoma assay. Ceftaroline was not mutagenic in an in vitro mammalian cell assay. In vivo, ceftaroline fosamil did not induce unscheduled DNA synthesis in rat hepatocytes and did not induce the formation of micronucleated erythrocytes in mouse or rat bone marrow. Both ceftaroline fosamil and ceftaroline were clastogenic in the absence of metabolic activation in an in vitro chromosomal aberration assays, but not in the presence of metabolic activation.

IV injection of ceftaroline fosamil had no adverse effects on fertility of male and female rats given up to 450 mg/kg. This is approximately 4-fold higher than the maximum recommended human dose based on body surface area.

14. Clinical Trials

14.1 Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

A total of 1396 adults with clinically documented complicated skin and skin structure infection were enrolled in two identical randomized, multi-center, multinational, double-blind, noninferiority trials (Trials 1 and 2) comparing Teflaro (600 mg administered IV over 1 hour every 12 hours) to vancomycin plus aztreonam (1 g vancomycin administered IV over 1 hour followed by 1 g aztreonam administered IV over 1 hour every 12 hours). Treatment duration was 5 to 14 days. A switch to oral therapy was not allowed. The Modified Intent-to-Treat (MITT) population included all patients who received any amount of study drug according to their randomized treatment group. The CE population included patients in the MITT population who demonstrated sufficient adherence to the protocol.

To evaluate the treatment effect of ceftaroline, an analysis was conducted in 797 patients with ABSSSI (such as deep / extensive cellulitis or a wound infection [surgical or traumatic]) for whom the treatment effect of antibacterials may be supported by historical evidence. This analysis evaluated responder rates based on achieving both cessation of lesion spread and absence of fever on Trial Day 3 in the following subgroup of patients:

Patients with lesion size ≥ 75 cm^2 and having one of the following infection types:

- Major abscess with ≥ 5 cm of surrounding erythema
- Wound infection
- Deep/extensive cellulitis

The results of this analysis are shown in Table 8.

Table 8: Clinical Responders at Study Day 3 from Two Phase 3 ABSSSI Trials

	Teflaro n/N (%)	Vancomycin/ Aztreonam n/N (%)	Treatment Difference (2-sided 95% CI)
ABSSSI Trial 1	148/200 (74.0)	135/209 (64.6)	9.4 (0.4, 18.2)
ABSSSI Trial 2	148/200 (74.0)	128/188 (68.1)	5.9 (-3.1, 14.9)

The protocol-specified analyses included clinical cure rates at the Test of Cure (TOC) (visit 8 to 15 days after the end of therapy) in the coprimary CE and MITT populations (Table 9) and clinical cure rates at TOC by pathogen in the Microbiologically Evaluable (ME) population (Table 10). However, there are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at a TOC time point. Therefore, comparisons of Teflaro to vancomycin plus aztreonam based on clinical response rates at TOC can not be utilized to establish non-inferiority.

Table 9: Clinical Cure Rates at TOC from Two Phase 3 ABSSSI Trials

	Teflaro n/N (%)	Vancomycin/ Aztreonam n/N (%)	Treatment Difference (2-sided 95% CI)
Trial 1			
CE	288/316 (91.1)	280/300 (93.3)	-2.2 (-6.6, 2.1)
MITT	304/351 (86.6)	297/347 (85.6)	1.0 (-4.2, 6.2)
Trial 2			
CE	271/294 (92.2)	269/292 (92.1)	0.1 (-4.4., 4.5)
MITT	291/342 (85.1)	289/338 (85.5)	-0.4 (-5.8, 5.0)

Table 10: Clinical Cure Rates at TOC by Pathogen from Two Integrated Phase 3 ABSSSI Trials

	Teflaro n/N (%)	Vancomycin/Aztreonam n/N (%)
Gram-positive:		
MSSA (methicillin-susceptible)	212/228 (93.0%)	225/238 (94.5%)
MRSA (methicillin-resistant)	142/152 (93.4%)	115/122 (94.3%)
Streptococcus pyogenes	56/56 (100%)	56/58 (96.6%)
Streptococcus agalactiae	21/22 (95.5%)	18/18 (100%)
Gram-negative:		
Escherichia coli	20/21 (95.2%)	19/21 (90.5%)
Klebsiella pneumoniae	17/18 (94.4%)	13/14 (92.9%)
Klebsiella oxytoca	10/12 (83.3%)	6/6 (100%)

14.2 Community-Acquired Bacterial Pneumonia (CABP)

A total of 1231 adults with a diagnosis of CABP were enrolled in two randomized, multi-center, multinational, double-blind, noninferiority trials (Trials 1 and 2) comparing Teflaro (600 mg administered IV over 1 hour every 12 hours) with ceftriaxone (1 g ceftriaxone administered IV over 30 minutes every 24 hours). In both treatment groups of CABP Trial 1, two doses of oral clarithromycin (500 mg every 12 hours), were administered as adjunctive therapy starting on Study Day 1. No adjunctive macrolide therapy was used in CABP Trial 2. Patients with known or suspected MRSA were excluded from both trials. Patients with new or progressive pulmonary infiltrate(s) on chest radiography and signs and symptoms consistent with CABP with the need for hospitalization and IV therapy were enrolled in the trials. Treatment duration was 5 to 7 days. A switch to oral therapy was not allowed. Among all subjects who received any amount of study drug in the two CABP trials, the 30-day all-cause mortality rates were 11/609 (1.8%) for the Teflaro group vs. 12/610 (2.0%) for the ceftriaxone group, and the difference in mortality rates was not statistically significant.

To evaluate the treatment effect of ceftaroline, an analysis was conducted in CABP patients for whom the treatment effect of antibacterials may be supported by historical evidence. The analysis endpoint required subjects to meet sign and symptom criteria at Day 4 of therapy: a responder had to both (a) be in stable condition according to consensus treatment guidelines of the Infectious Diseases Society of America and American Thoracic Society, based on temperature, heart rate, respiratory rate, blood pressure, oxygen saturation, and mental status;[4] (b) show improvement from baseline on at least one symptom of cough, dyspnea, pleuritic chest pain, or sputum production, while not worsening on any of these four symptoms. The analysis used a microbiological intent-to-treat population (mITT population) containing only subjects with a confirmed bacterial pathogen at baseline. Results for this analysis are presented in Table 11.

Table 11: Response Rates at Study Day 4 (72-96 hours) from Two Phase 3 CABP Trials

	Teflaro n/N (%)	Ceftriaxone n/N (%)	Treatment Difference (2-sided 95% CI)
CABP Trial 1	48/69 (69.6%)	42/72 (58.3%)	11.2(-4.6,26.5)
CABP Trial 2	58/84(69.0%)	51/83 (61.4%)	7.6 (-6.8,21.8)

The protocol-specified analyses included clinical cure rates at the TOC (8 to 15 days after the end of therapy) in the coprimary Modified Intent-to-Treat Efficacy (MITTE) and CE populations (Table 12) and clinical cure rates at TOC by pathogen in the Microbiologically Evaluable (ME) population (Table 13). However, there are insufficient historical data to establish the magnitude of drug effect for antibacterials drugs compared with placebo at a TOC time point. Therefore, comparisons of Teflaro to ceftriaxone based on clinical response rates at TOC cannot be utilized to establish non-inferiority. Neither trial established that Teflaro was statistically superior to ceftriaxone in terms of clinical response rates. The MITTE population included all patients who received any amount of study drug according to their randomized treatment group and were in PORT (Pneumonia Outcomes Research Team) Risk Class III or IV. The CE population included patients in the MITTE population who demonstrated sufficient adherence to the protocol.

Table 12: Clinical Cure Rates at TOC from Two Phase 3 CABP Trials

	Teflaro n/N (%)	Ceftriaxone n/N (%)	Treatment Difference (2-sided 95% CI)
CABP Trial 1			
CE	194/224 (86.6%)	183/234 (78.2%)	8.4 (1.4, 15.4)
MITTE	244/291 (83.8%)	233/300 (77.7%)	6.2 (-0.2, 12.6)
CABP Trial 2			
CE	191/232 (82.3%)	165/214 (77.1%)	5.2 (-2.2, 12.8)
MITTE	231/284 (81.3%)	203/269 (75.5%)	5.9 (-1.0, 12.8)

Table 13: Clinical Cure Rates at TOC by Pathogen from Two Integrated Phase 3 CABP Trials

	Teflaro n/N (%)	Ceftriaxone n/N (%)
Gram-positive:		
Streptococcus pneumoniae	54/63 (85.7%)	41/59 (69.5%)
Staphylococcus aureus (methicillin-susceptible isolates only)	18/25 (72.0%)	14/25 (56.0%)
Gram-negative		
Haemophilus influenzae	15/18 (83.3%)	17/20 (85.0%)
Klebsiella pneumoniae	12/12 (100%)	10/12 (83.3%)
Klebsiella oxytoca	5/6 (83.3%)	7/8 (87.5%)
Escherichia coli	10/12 (83.3%)	9/12 (75.0%)

15. References

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - 8th ed. Approved Standard, CLSI document M07-A8, CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898. January 2009.

2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests 10th ed. Approved Standard, CLSI document M02-A10, CLSI, January 2009.

3. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing 20th Informational Supplement, CLSI document M100-S20, CLSI, January 2010.

4. Mandell, L.A., Wunderink, R.G., Anzueto, A., Bartlett, J.G., Campbell, G.D., Dean, N.C., Dowell, S.F., File, T.M., Musher, D.M., Niederman, M.S., Torres, A., Whitney, C.G. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clinical Infectious Disease. 2007; 44:S27-72.

16. How Supplied/Storage and Handling

Teflaro (ceftaroline fosamil) for injection is supplied in single-use, clear glass vials containing:

- 600 mg - individual vial (NDC 0456-0600-01) and carton containing 10 vials (NDC 0456-0600-10)
- 400 mg - individual vial (NDC 0456-0400-01) and carton containing 10 vials (NDC 0456-0400-10)

Teflaro vials should be stored refrigerated at 2 to 8° C (36 to 46° F).

17. Patient Counseling Information

- Patients should be advised that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. They should inform their healthcare provider about any previous hypersensitivity reactions to Teflaro, other beta-lactams (including cephalosporins) or other allergens.
- Patients should be counseled that antibacterial drugs including Teflaro should be used to treat only bacterial infections. They do not treat viral infections (e.g., the common cold). When Teflaro is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Teflaro or other antibacterial drugs in the future.
- Patients should be advised that diarrhea is a common problem caused by antibacterial drugs and usually resolves when the drug is discontinued. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, patients should contact their healthcare provider.
- Keep out of reach of children

Teflaro (ceftaroline fosamil) for injection

Distributed by:

Forest Pharmaceuticals, Inc.

Subsidiary of Forest Laboratories, Inc.

St. Louis, MO 63045, USA

Manufactured by:

Facta Farmaceutici S.p.A.

Nucleo Industriale S. Atto–S. Nicolò a Tordino

64020 Teramo, Italy

Teflaro is a trademark of Forest Laboratories, Inc.

Label Part Number

Revised: [month year]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDWARD M COX
10/29/2010

EXHIBIT E

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200327

NDA APPROVAL

Cerexa, Inc.
Attention: Bruce Lu, R.Ph., RAC
Senior Director, Regulatory Affairs
2100 Franklin St., Suite 900
Oakland, CA 94612

Dear Mr. Lu:

Please refer to your New Drug Application (NDA) dated December 29, 2009, received December 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Teflaro (ceftaroline fosamil) for Injection.

We acknowledge receipt of your amendments dated January 8, 20, 26 and 29; February 2 and 4, April 14, 23(2), 28, 29 and 30; May 3 and 14; June 2, 7, 18, 21 and 23; July 2, 9, 13, 14, 20 and 27; August 2(2), 4, 6, 9, 10, 18, 19, 20, 24 and 30; September 16, 20, 21 and 24; and October 13(2), 14, 18(2), 20 and 28(2), 2010.

This new drug application provides for the use of Teflaro (ceftaroline fosamil) for Injection for the treatment of Acute Bacterial Skin and Skin Structure Infections and Community Acquired Bacterial Pneumonia.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your October 14, 2010 submission containing carton and container labels.

Submit final printed carton and container labels that are identical to the carton labels submitted on October 14, 2010 and the immediate container labels submitted on October 20, 2010 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 200327**". Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred or inapplicable.

We are deferring submission of pediatric trials in patients aged 0 to 17 years for Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and Community-Acquired Bacterial Pneumonia (CABP) until July 2015, because this product is ready for approval for use in adults and pediatric trials have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below:

1692-001: Single dose pharmacokinetic trial

Perform a trial in pediatric patients being treated concomitantly with antibacterial agent(s) to evaluate single dose pharmacokinetic parameters and assess safety of Teflaro (ceftaroline fosamil) in all pediatric age groups. Five age cohorts must be studied as follows:

- Group 1: children from 6 to less than 12 years
- Group 2: children from 24 months to less than 6 years
- Group 3: infants/toddlers from 28 days to less than 24 months

- Group 4: term neonates less than 28 days; (stratification within the group: 0-14 days; >14 days to <28 days)
- Group 5: pre-term neonates less than 28 days (stratification within the group: 0-14 days; >14 days to <28 days)

There must be a minimum of 8 evaluable subjects per cohort. In Group 3, there will be an equal representation of patients aged 28 days to <12 months and ≥12 months to <24 months.

Final Protocol Submission: 11/2010
Trial Completion Date: 01/2014
Final Report Submission: 07/2014

1692-002: Perform a randomized comparison of Teflaro (ceftaroline fosamil) and comparator in pediatric subjects with CABP utilizing an enrichment strategy for enrollment of patients with methicillin-resistant *Staphylococcus aureus* (MRSA). Pediatric patients under 17 years of age with CABP must be enrolled, with a minimum of 150 patients receiving Teflaro (ceftaroline fosamil).

Final Protocol Submission: 09/2011
Trial Completion Date: 05/2014
Final Report Submission: 11/2014

1692-003: Perform a randomized comparison of Teflaro (ceftaroline fosamil) and comparator in pediatric subjects with ABSSSI including patients with infection suspected or demonstrated to be caused by MRSA. Pediatric patients under 17 years of age with ABSSSI must be enrolled, with a minimum of 150 patients receiving Teflaro (ceftaroline fosamil).

Final Protocol Submission: 09/2011
Trial Completion Date: 05/2014
Final Report Submission: 11/2014

1692-004: Cerebrospinal Fluid (CSF) Concentration Trial

Perform a trial assessing the CSF concentration profile of Teflaro (ceftaroline fosamil) in infants < 2 months of age. A minimum of 12 infants < 2 months of age receiving antibacterials for treatment of late-onset neonatal sepsis must be studied.

Final Protocol Submission: 05/2014
Trial Completion Date: 09/2016
Final Report Submission: 03/2017

1692-005: Perform a randomized comparison of Teflaro (ceftaroline fosamil) and comparator in infants < 2 months of age with ABSSSI and CABP including patients with infections suspected or demonstrated to be caused by MRSA.

Final Protocol Submission: 05/2014
Trial Completion Date: 09/2016
Final Report Submission: 03/2017

Submit final reports to the NDA. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessments**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of serious risk of development of bacterial resistance.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1692-006: Conduct a prospective study over a five-year period after introduction of Teflaro (ceftaroline fosamil) to the market to determine if decreased susceptibility to Teflaro (ceftaroline fosamil) is occurring in the target bacteria included in the Indications section of the approved Teflaro (ceftaroline fosamil) package insert. Provide a detailed protocol describing the study to the Agency for review and comment before commencing the study.

The timetable you submitted on October 14, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 01/2011
First Interim Report: 10/2011, and then annually until 10/2015
Study Completion: 04/2016
Final Report Submission: 10/2016

Submit the protocol to your IND 71,371, with a cross-reference letter to this NDA. Submit all interim and final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate

"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment in your submission dated October 14, 2010. This commitment is listed below:

1692-007: Conduct a prospective, randomized trial evaluating the efficacy and safety of Teflaro (ceftaroline fosamil) versus comparator in the treatment of patients with CABP at high risk for infection caused by MRSA.

Final Protocol Submission: 10/2011
Trial Completion Date: 09/2016
Final Report Submission: 04/2017

Submit clinical protocols to your IND 71,371 for this product. Submit nonclinical and chemistry, manufacturing, and control protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trial, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol,**" "**Postmarketing Commitment Final Report,**" or "**Postmarketing Commitment Correspondence.**"

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, MD., MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDWARD M COX
10/29/2010

EXHIBIT F

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 000000 ISTMT DATE PRINTED 11/08/2010

TAKEDA PHARMACEUTICALS NORTH AMERICA, IN
INTELLECTUAL PROPERTY DEPARTMENT
ONE TAKEDA PARKWAY
DEERFIELD IL 60015

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,417,175	**$900.00**	**$0.00**	**12/16/05**	**09/555,949**	**07/09/02**	**06/06/00**	**04**	**NO**	**2499USOP**

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 000000 | ISTMT | DATE PRINTED 11/04/2010

TAKEDA PHARMACEUTICALS NORTH AMERICA, IN
INTELLECTUAL PROPERTY DEPARTMENT
ONE TAKEDA PARKWAY
DEERFIELD IL 60015

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,417,175	**$2,480.00**	**$0.00**	**12/09/09**	**09/555,949**	**07/09/02**	**06/06/00**	**08**	**NO**	**TAKEDA CHEMICAL INDUSTRIE**

EXHIBIT G

Peninsula
PHARMACEUTICALS, INC.

10 December 2004

Janice Soreth, M.D.
Division Director, Division of Anti-Infective Drug Products
Food & Drug Administration
Office of Drug Evaluation IV (HFD-104)
Attn: Ms. Frances LeSane
9201 Corporate Blvd, 4th Floor
Rockville, MD 20850

Re: Investigational New Drug Application
PPI-0903
Serial Number: 000

Dear Dr. Soreth,

Pursuant to 21 CFR § 312.20, enclosed in triplicate is the Investigational New Drug Application for PPI-0903.

Peninsula Pharmaceuticals, Inc. (PPI) plans to develop PPI-0903 as a broad spectrum cephalosporin antibiotic for the treatment of serious bacterial infections, including community-acquired pneumonia (CAP) and skin and skin structure infections (SSSI), that may be caused by a broad range of gram-negative and resistant gram-positive bacteria, including penicillin-resistant *Streptococcus pneumoniae* (PRSP) and methicillin-resistant *Staphylococcus aureus* (MRSA).

PPI-0903 is a sterile, synthetic, parenteral pro-drug of a novel cephalosporin class of beta-lactam antibiotics. The pro-drug (PPI-0903) is rapidly metabolized into a bioactive metabolite which exhibits antibacterial activity. PPI-0903 displays broad *in vitro* bactericidal activity against aerobic and anaerobic gram-positive and gram-negative bacteria.

New antibiotics are needed to treat serious as well as common infections caused by bacteria that are becoming increasingly resistant to currently available therapies. PPI believes that current *in vitro* and *in vivo* microbiological data support the clinical development of PPI-0903 as a potential human therapeutic agent against serious gram-positive and gram-negative bacterial infections.

PENINSULA PHARMACEUTICALS, INC. • 1751 HARBOR BAY PARKWAY • ALAMEDA, CALIFORNIA 94502 • TEL: (510) 747-3900 FAX: (510) 747-3940

PPI understands that clinical investigations subject to § 312.2(a) will not proceed until the investigation is subject to an IND which is in effect in accordance with § 312.40. PPI is looking forward to working with FDA on this project.

Should you have any questions regarding this submission, please do not hesitate to contact me directly at (510) 747-3904.

Sincerely,

Ursula Fritsch, Pharm.D.
Sr. Director, Global Regulatory Affairs
Peninsula Pharmaceuticals, Inc.
Office: 510-747-3904 Facsimile: 510-747-3940

Enclosure: 32 volumes of PPI-0903 IND, in triplicate (96 volumes total)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Peninsula Pharmaceuticals, Inc.

2. DATE OF SUBMISSION
12/10/04

3. ADDRESS *(Number, Street, City, State and Zip Code)*
1751 Harbor Bay Parkway
Alameda, CA 94502

4. TELEPHONE NUMBER *(Include Area Code)*
510-747-3904

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
PPI-0903, or:

((6R,7R)-7-(((2Z)-(ethoxyimino)-2-(5-(phosphonoamino)-1,2,4-thiadiazol-3-yl)acetyl)amino)-3-((4-(1-methyl-4-pyridiniumyl)-1,3-thiazol-2-yl)sulfanyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, acetic acid solvate, monohydrate

6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*
Serious bacterial infections

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☒ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
0 0 0

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☒ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

1-1

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☒ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☒ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☒ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☒ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☒ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☒ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☒ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☒ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☒ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☒ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☒ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Rebecca Redman, MD
Sr. Director, Clinical Development

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

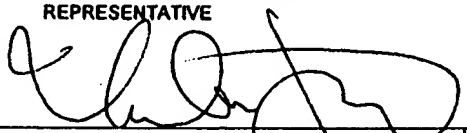
Sally Van Doren, Pharm.D.
Sr. Director, Drug Safety

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

Ursula Fritsch, Pharm.D.
Sr. Director, Global Regulatory Affairs

17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE



18. ADDRESS *(Number, Street, City, State and Zip Code)*

1751 Harbor Bay Parkway
Alameda, CA 94502

19. TELEPHONE NUMBER *(Include Area Code)*

510-747-3904 office
510-747-3940 facsimile

20. DATE

12/10/04

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this application to this address.

EXHIBIT H

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 71,371

Peninsula Pharmaceuticals, Inc.
Attention: Sharon K. Powell, PhD
Manager, Regulatory Affairs
1701 Harbor Bay Parkway
Alameda, CA 94502

Dear Dr. Powell:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 71,371

Sponsor: Peninsula Pharmaceuticals, Inc.

Name of Drug: PPI-0903

Date of Submission: December 10, 2004

Date of Receipt: December 13, 2004

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to either one of the following addresses:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products, HFD-520
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products, HFD-520
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions, call Judit Milstein, Regulatory Health Project Manager, at (301) 827-2207.

Sincerely,

{See appended electronic signature page}

Frances LeSane
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Frances LeSane
3/3/05 10:47:21 AM

EXHIBIT I

Peninsula
PHARMACEUTICALS, INC.

30 June 2005

Janice Soreth, M.D.
Division Director, Division of Anti-Infective Products
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Products, HFD-520
Attn: Division Document Room
9201 Corporate Blvd
Rockville, MD 20850

RE: IND 71, 371
PPI-0903
Other: Transfer of IND Sponsorship
Serial Number: 014

Dear Dr. Soreth,

As of June 30, 2005, all rights to and responsibilities for IND 71, 371 are transferred from Peninsula Pharmaceuticals, Inc. to Cerexa, Inc. Cerexa has been given a complete copy of the original IND (submitted on 10 December 2004), all subsequent amendments and correspondence. The name, address, and telephone/facsimile number for the Cerexa contact for the IND are as follow:

Mary O'Hara-Zimmerman
Acting Head of Regulatory Affairs
Cerexa, Inc.
1751 Harbor Bay Parkway
Alameda, CA 94502
TEL: 510-747-3900
FAX: 510-747-3940

Sincerely,

Sharon K. Powell, Ph.D.
Manager, Regulatory Affairs
Peninsula Pharmaceuticals, Inc.
Office: 510-747-3918 Facsimile: 510-747-3940

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Peninsula Pharmaceuticals, Inc.

2. DATE OF SUBMISSION
06/30/05

3. ADDRESS *(Number, Street, City, State and Zip Code)*
1751 Harbor Bay Parkway
Alameda, CA 94502

4. TELEPHONE NUMBER *(Include Area Code)*
510-747-3918

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
PPI-0903, or:

((6R,7R)-7-(((2Z)-(ethoxyimino)-2-(5-(phosphonoamino)-1,2,4-thiadiazol-3-yl)acetyl)amino)-3-((4-(1-methyl-4-pyridiniumyl)-1,3-thiazol-2-yl)sulfanyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, acetic acid solvate, monohydrate

6. IND NUMBER *(If previously assigned)*
71,371

7. INDICATION(S) *(Covered by this submission)*
Serious bacterial infections

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☒ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

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☐ RESPONSE TO CLINICAL HOLD

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☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
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IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

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☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
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☐ **TREATMENT IND 21 CFR 312.35(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35(a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)**

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

12. **CONTENTS OF APPLICATION**

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IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Rebecca Redman, MD
Sr. Director, Clinical Development

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Sally Van Doren, Pharm.D.
Sr. Director, Drug Safety

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Sharon Powell, Ph.D. Manager, Regulatory Affairs	Sharon Kay Powell	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
1751 Harbor Bay Parkway Alameda, CA 94502	510-747-3918 office 510-747-3940 facsimile	06/30/05

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od and Drug Administration
ER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

EXHIBIT J

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 71,371

Cerexa, Inc.
Attention: Mary O'Hara-Zimmerman
Acting Head, Regulatory Affairs
1751 Harbor Bay Parkway
Alameda, CA 94502

Dear Ms O'Hara-Zimmerman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PPI-0903.

Reference is also made to the June 30, 2005; submission notifying us that the rights and responsibilities for this IND have been transferred from Peninsula Pharmaceuticals, Inc. to Cerexa, Inc.

Your submission contains all the information required to complete the change in sponsorship. Our files will be updated to list Cerexa, Inc. as the sponsor of this IND.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

If you have any questions, call Carmen DeBellas, Project Manager, at 301-827-2125.

Sincerely,
{See appended electronic signature page}

Frances Le Sane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology
Products, HFD-520
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc: Peninsula, Pharmaceuticals, Inc
Attention: Sharon K. Powell, Ph.D
Manager, Regulatory Affairs
1751 Harbor Bay Parkway
Alameda, CA 94502

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Frances LeSane
7/14/05 05:15:06 PM

EXHIBIT K

CEREXA

A subsidiary of Forest Laboratories, Inc.

30 December 2009

Food and Drug Administration
Center for Drug Evaluation and Research
Electronic Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

ATTN: Wiley Chambers, M.D.
Director (Acting)
Division of Anti-Infective and Ophthalmology Products (DAIOP)
10903 New Hampshire Avenue
Building WO22, Room 6366
Silver Spring, MD 20993

RE: NDA 200327, APTARIN™, Ceftaroline Fosamil for Injection
Original Submission for a Prescription Drug Product

Dear Dr. Chambers:

Cerexa, Inc. a wholly-owned subsidiary of Forest Laboratories, Inc, hereby submits an original New Drug Application (NDA) in the eCTD format for APTARIN™, Ceftaroline Fosamil for Injection, 400mg and 600mg, pursuant to the requirements of section 505(b)(l) of the Federal Food, Drug, and Cosmetic Act (act), Section 314.50 of the United States Code of Federal Regulations (CFR) and supporting Food and Drug Administration guidelines.

Please note that throughout this NDA, the Sponsor may be referred to as Cerexa, Inc. or Forest Laboratories, Inc. Both Cerexa, Inc. and Forest Laboratories, Inc. are considered interchangeable for review purposes.

APTARIN is being developed by Cerexa, Inc and Forest Laboratories, Inc for the treatment of complicated skin and skin structure infection (cSSSI) and community-acquired bacterial pneumonia (CABP) caused by designated susceptible bacteria. Cerexa has conducted an extensive clinical program with APTARIN under IND 71,371, during which there have been a number of discussions and agreements reached with the Agency (see Module 1, Section 1.6.3). The clinical development program for APTARIN is comprised of 17 clinical studies in which a total 1706 healthy subjects and patients, including adults, adolescents, subjects with mild, moderate, and severe renal impairment, end-stage renal disease (ESRD) receiving hemodialysis, and subjects with cSSSI and CABP, have been exposed to APTARIN. Across these studies, the data demonstrate that APTARIN is an effective, safe, and well-tolerated treatment for cSSSI and CABP.

As a preface to the NDA 200327 submission, this cover letter contains information regarding the following:

- Submission structure and data format
- Request for priority review
- Request for exclusivity
- Request for trade name approval
- ECG Datasets
- The 4-Month Safety Update

Submission Structure and Format

The structure of this submission is based on the eCTD format in accordance with the "Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications" October 2005 and according to specifications provided in "ICH M2 EWG Electronic Common Technical Document Specification -- ICH eCTD Specification V3.2.2 16-July-2008"

The size of the electronic submission is approximately 10.8 gigabytes. The eCTD is provided through FDA's Electronic Submissions Gateway system. All files in this electronic submission have been verified to be virus free as of December 29, 2009 by the following antivirus program:

Software: McAfee VirusScan Enterprise 8.7.0.570

The raw data adheres to the CDISC Study Data Tabulation Model (STDM). The SDTM datasets were prepared in accordance with the SDTM Implementation Guide for Human Clinical Trials version 3.1.1 (SDTMIG 3.1.1).

As agreed with Agency, Module 5 Integrated Summaries of Efficacy (ISE) and Module 2 Summary of Clinical Efficacy (SCE) are presented per indication: one for cSSSI and one for CABP respectively. The NDA also includes one Integrated Summary of Safety (ISS) report that consist of both cSSSI and CABP indications.

Request for Priority Review

As stipulated in the FDA Manual of Policies and Procedures (CDER, Office of New Drugs, MAPP 6020.3) Cerexa believes APTARIN is eligible for priority review. A formal request for priority review designation for APTARIN is provided in Module 1, Section 1.7.1.

Request for Exclusivity

Pursuant to 21 CFR 314.50(j) and with reference to 21 CFR 314.108 (b)(2), Cerexa is requesting exclusivity for APTARIN. A formal request for exclusivity is provided in Module 1, Section 1.3.5.3.

Request for Trade Name Approval

For NDA 200327, Cerexa is proposing APTARIN as the primary proprietary name. Cerexa will submit the proprietary name for review according to the Guidance for Industry "Contents of a Complete Submission for the Evaluation of Proprietary Names" Draft Guidance November 2008, after submission of the NDA.

The ECG Datasets

Reference is made to an October 8, 2009 email from Carmen DeBellas, Pharm D. RPh., Project Manager, Division of Anti-Infective and Ophthalmology Products, Center for Drug Evaluation and Research. It was agreed that the annotated electrocardiograms (ECG) datasets for Cerexa's "thorough QT/QTc study" P903-05 will be accessible to the FDA after the submission of the NDA. FDA will be able to access the annotated ECG dataset through the Mortara E-Scribe ECG Warehouse.

The 4-Month Safety Update

Cerexa shall, under section 505(i) of the act and 21 CFR 314.50(d)(5)(vi), update its pending application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. Cerexa shall submit a safety update report four months after the initial submission. Prior to the submission of the safety update report, Cerexa will consult with FDA regarding further details on its form and content.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C. Section 331 (J).

The primary Regulatory Affairs contact for this NDA is Steffany Gaffagan, Sr. Manager Regulatory Affairs: telephone 510-285-9220, facsimile 510-285-9482, and e-mail sgaffagan@cerexa.com. The technical contact for matters concerning the operation and navigation of the eCTD is Wendy Gill, Assistant Director, Regulatory Affairs: telephone 201-386-2125, facsimile 201-524-9711, and e-mail wendy.gill@frx.com. If there are any questions with respect to this submission, please contact me or either of my colleagues.

Kind Regards,

Bruce Lu, RPh, RAC
Sr. Director, Regulatory Affairs
telephone 510-285-9325
facsimile 510-285-9482
e-mail blu@cerexa.com

EXHIBIT L

Interactions with the FDA

Date of meeting/ correspondence	Program	Description of meeting/correspondence
10 December 2004	Phase 1 cSSSI	Original IND submitted for P903-02
5 April 2005	Phase 1 cSSSI	Division comments on IM study, age and gender
05 August 2005	Phase 1 and 2 cSSSI	Division comments on protocol P903-01, -02, -03 and general comments on overall program (elderly, drug-drug interaction)
28 February 2006	cSSSI indication	Division grants Fast Track designation for cSSSI
24 October 2006	Phase 3 CABP, cSSSI	Teleconference - EOP2 Meeting
07 February 2007	Phase 3 cSSSI	Division comments on NI justification
15 March 2007	Phase 3 CABP	Division comments on CABP SPA
01 June 2007	Phase 3 CABP, cSSSI	Face-to-face meeting cancelled. Division's comments to questions posed in meeting request via email. Division's recommendation to revise P903-08 to allow only 24 hours of adjunctive clarithromycin with no option for oral switch; the acceptance of NI margin justification deferred
07 June 2007	Phase 3 CABP	Final clinical and statistical comments on study design (not including NI margin)
31 July 2007	Phase 1 ECG	Division's comments on ECG study P903-05
11 September 2007	Phase 3 CABP	Division comment on NI margin
02 November 2007	Phase 3 CABP	Teleconference - Type A meeting with Division regarding the P903-08 and P903-09 protocol design
08 January 2009	Phase 3 CABP	FDA comments on P903-08 and P903-09 CABP SAP
09 April 2009	Phase 3 cSSSI	FDA comments on P903-06 and P903-07 cSSSI SAP
07 July 09	all clinical and nonclinical studies	Face-to-face - Type B clinical and preclinical preNDA meeting
22 July 2009	CMC	Face-to-face - Type B CMC preNDA meeting
12 December 2009	Phase 3 cSSSI	Teleconference - Discussion on P903-06 sample datasets
01 June 2010	Phase 3 CABP, cSSSI	Teleconference - Discussion on sensitivity analysis
07 September 2010	CABP, cSSSI indication	AC meeting for CABP and cSSSI
15 October 2010	Label and Phase 4	Teleconference - Discussion with Division on Ceftaroline label negotiation and Post market commitment and Post market requirement
27 October 2010	Label and Phase 4	Teleconference - Discussion with Division on Ceftaroline label negotiation and Post market commitment and Post market requirement
29 October 2010	NDA 200327 action letter	Received action letter

Clinical Studies: First Subject Enrolled and Last Subject/Last Visit

Study	First Subject Enrolled (study initiation)	Last Subject/Last Visit (completion of the study)
Phase 1 Study		
P903-01	12 May 2004	13 Sep 2004
P903-02	11 Feb 2005	28 Feb 2006
P903-04	28 Apr 2007	06 Jun 2008
P903-05	13 Jun 2008	01 Aug 2008
P903-11	18 Feb 2008	25 Jun 2008
P903-13	09 Jan 2008	07 Feb 2008
P903-14	02 Oct 2008	03 Dec 2008
P903-15	29 Apr 2008	12 Feb 2009
P903-17	21 Jun 2007	27 Aug 2007
P903-18	18 Oct 2007	31 Jan 2008
P903-20	10 Nov 2007	23 Dec 2007
Phase 2 Study		
P903-03	14 Oct 2005	10 May 2006
Phase 3 Study		
P903-06	27 Feb 2007	07 Nov 2007
P903-07	01 Mar 2007	19 Dec 2007
P903-08	02 Jan 2008	29 Dec 2008
P903-09	04 Jul 2007	27 Aug 2008

Ceftaroline IND
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IND CORRESPONDENCE LOG

Date of Correspondence	Book No.	Communication Type	Description	Protocol
15-Dec-04	A	General	Fax: PPI to FDA:IND coverletter	
13-Jan-05	A	General	Change IND Contact	
14-Jan-05	A	Response/Comments	Comments on original IND Clinical, Pharmacology, Chemistry, Micro See #013 for response.	
24-Jan-05	A	General	Request official notification of IND receipt.	
24-Jan-05a	A	Response/Comments	OK to proceed with Ph1 study.	
25-Jan-05	A	General	Confirmation that record of contact for 24Jan2005 TC was accurate.	
03-Mar-05	A	FDA Letter	Acknowledging receipt of IND	
10-Mar-05	A	Response/Comments	Clarify correct IND mailing address, request comments from FDA on study P903-03, request "official" comments from FDA.	
08-Apr-05	A	FDA Letter	Official comments on original IND submission previously sent on 14 Jan 2005 See #013 for response.	Original IND
11-Apr-05	A	General	Request status of comments on P903-03	P903-03
11-Apr-05-a	A	FDA Letter	Comments on original IND submission previously sent on 14 Jan 2005 See #013 for response.	Original IND
18-Apr-05	A	Response/Comments	Request for in vitro genotox study with metabolite, 3-mo tox study-See #021 for response.	
03-May-05	A	Response/Comments	Comments on P903-03 (CNS exclusion, choice of comparators, screening window, clinical failures, Coombs test, extension of tx, causality assessment, SAE F/U, microbiologic endpoints and assessment of efficacy)-See #021 for response.	P903-03
11-Jul-05	A	General	Clarification of number of ECG evaluations P903-02. Confirmed that baseline ECG recordings be in triplicate, subsequent recordings are single.	P903-02
14-Jul-05	A	General	Re-sending email of 03 May 05	
14-Jul-05a	A	General	Introduction to PM at FDA, request understanding of FDA forms of communication and documentation	
14-Jul-05b	A	General	Re-sending email of 18 April 05. May resend comments as "Advice Letter."	
14-Jul-05c	A	FDA Letter	Acknowledge change of IND Sponsorship from Peninsula to Cerexa.	

05-Aug-05	A	FDA Letter	Comments on P903-03(previously emailed); in vitro genotox study (previously emailed); New comment on Micro. Manual and Gram stain procedure. See #021 for response	P903-03; IND
8-Sep-05	A	General	Informed Division of forthcoming submissions (P903-03 final protocol, initial investigator, response letter)	
12-Sep-05	A	General	email PDF copy of #019 (P903-03 Protocol); #020 (P903-03 New Investigator); #021 (Response to FDA Letter)	P903-03; IND
3-Oct-05	A	General	PDF copy of #019 (P903-03 Protocol)	P903-03
6-Jan-06	A	General	Forwarding electronic copy of #028: Request for Fast Track Destination	
12-Jan-06	A	FDA Letter	Confirm receipt of Fast Track Designation Submission	
28-Feb-06	A	FDA Letter	Fast Track Designation Granted for PPI-0903 for cSSSI (including MRSA)	
14-Jun-06	A	General	Requesting FDA feedback on proposed content of EOP2 mtg and development plan	Phase 3 Development
30-Jun-06	A	General	Response to 14 June 05 email: cSSSI protocol be submitted as part of EOP2 meeting package.	Phase 3 Development; EOP2
1-Aug-06	A	General	Forwarding End of Phase 2 Meeting Requests (#043 and #044)	EOP2
9-Aug-06	A	FDA Letter	EOP2 Meeting Date	
21-Aug-06	A	General	FDA declined request for a CMC meeting as the information submitted was straightforward (#043)	
08/21/2006a	A	General	Request to reschedule the EOP2 meeting for the week of 16 October.	
22-Aug-06	A	FDA Letter	Formally declining CMC meeting request. FDA states meeting is unnecessary.	
25-Aug-06	A	FDA Letter	Confirm new date of 24Oct06 for EOP2 meeting.	
1-Sep-06	A	General	Clarification of EOP2 BB submission due date	
19-Sep-06	A	General	Email: FDA to Cerexa: send electronic copy of P3 cSSSI protocol	
25-Sep-06	A	General	CMC question will not be answered at clinical EOP2 mtg	
19-Oct-06	A	General	EOP2 mtg logistics	
20-Oct-06	A	Response/Comments	FDA response to EOP2 questions, provide draft micro guidance document	
20-Oct-06a	A	Response/Comments	Request for clarification on EOP2 responses. Attachment FDA Response to Cerexa Questions EOP2	

20-Oct-06b	A	Response/Comments	Request for clarification on EOP2 responses. Attachment Clinical Comments from EOP2	
20-Oct- 06c	A	Response/Comments	Request for clarification on EOP2 responses. Attachment Antibacterial Drug Development Guidance	
23-Oct-06	A	Response/Comments	Response to clarification, draft EOP2 Agenda	
23-Oct-06a	A	General	Change EOP2 mtg to telecom	
27-Oct-06	A	Cerexa Meeting Minutes	Internal Executive Summary of the EOP2 teleconference with FDA held on 24 October 2006	
3-Nov-06	A	General	Response to EOP2 comments delayed	
14-Nov-06	A	General	Submission logistics for TET Protocol	P903-05
16-Nov-06	A	Response/Comments	Microbiology Comments for P903-06 and -07	
21-Nov-06	A	Meeting Minutes	Official FDA meeting minutes of teleconference held 24Oct06	EOP2
18-Jan-07	A	Response/Comments	References requested for cSSSI NI margin justification	
31-Jan-07	A	FDA Letter	Acknowledgement of receipt for request for special Protocol Assessment for protocols P903-08 and P903-09	
7-Feb-07	A	Response/Comments	CSSI NI margin justification	
9-Feb-07	A	General	Clarification that 07 FEB 07 comments are just clinical and stats	
21-Feb-07		Response/Comments	Microbiology comments from FDA	
9-Mar-07	A	Response/Comments	Requesting references for CAP NI margin justification	
15-Mar-07	A	FDA Letter	Response to questions submitted with SPA for P903-08 and P903-09 study design	
16-Mar-07		Response/Comments	cSSSI NI margin justification	
16-Mar-07 a		General	email providing 15-Mar-07 FDA letter	
26-Mar-07	A	Response/Comments	Micro Comments EOP2	
26 MAR 07a	A	General	Request CD for #067	
26 MAR 07b	A	General	Meeting logistics to discuss cSSSI and CAP NI margin justification	
26 APR 07 b	A	General	Seeking advice how to proceed with "cSSSI risk" statement, possible conversation with Dr. Soreth	
27-Apr-07	A	FDA Letter	Type A Meeting scheduled for June 7, 2007 (to discuss cSSSI and CAP NI margin justification)	
21-May-07	A	General	Meeting material logistics to discuss cSSSI and CAP NI margin justification	
21-May-07a	A	General	QT protocol being reviewed by QT review team	
23-May-07	A	General	Division requesting meeting to discuss 07Jun07 meeting materials	P903-06, P903-07

23-May-07a	A	General	Meeting arranged with Dr. Soreth scheduled to discuss 07Jun07 meeting materials	P903-06, P903-07
23-May-07b	A	General	Division request #070 and #077 and original NI margin justification for cSSSI	P903-06, P903-07
23-May-07c	A	General	FDA Telecon Re. Minutes from a Division-requested telecom re. 07Jun07 meeting material.	P903-06, P903-07
01-Jun-07	A	General	Logistics of Continuous Marketing Application	
01-Jun-07a	A	Response/Comments	Response to questions in Type A meeting request (Regarding meeting logistics for FDA (internal only) briefing	
04-Jun-07	A	General	Possible cancellation of meeting	
05-Jun-07	A	General	Clarification on proposed meeting	
06-Jun-07	A	General	Update on clinical comment status	
07-Jun-07	A	Response/Comments	Clinical and statistical comments on CAP SPA	P903-08, P903-09
08-Jun-07	A	General	Comments of 07 June 07 received	P903-08, P903-09
18-Jun-07	A	General	Pediatric Study request logistics	P903-15
20-Jun-07	A	General	TET protocol review logistics	P903-05
21-Jun-07	A	General	Request for IB for TET review team	P903-05
21-Jun-07a	A	General	Comments to the IRT group	P903-05
21 JUN 07 b	A	General	Request for SAP for TET protocol for review team	P903-05
22-Jun-07	A	Meeting Minutes	Meeting Minutes from telephone call on 23 May 2007 re: meeting material NI for cSSSI, CAP study design and objective	P903-06, P903-07, P903-08, P903-09
07-Jul-07	A	General	One IND for both IV and IM	
18-Jul-07	A	General	Enrollment status for CAP	
31-Jul-07	A	Response/Comments	TET comments from Division and IRT group	P903-05
01-Aug-07	A	General	Clarification on comment 7 of TET comments	P903-05
02-Aug-07	A	General	Request status of final comments for NI margin justification for CAP	
15-Aug-07	A	General	Correction of submission address and requirement for color binders	
24-Aug-07	A	Safety	7-day alert reported to FDA-CRXA2007000040	
24-Aug-07a	A	General	Confirmation of IND amendment submission process and receipt of Pediatric Plan	
31-Aug-07	A	General	Further discussion IND amendment submission process and desk copies	
11-Sep-07	A	Response/Comments	CAP NI margin justification comment	
25-Sep-07	A	General	Request for meeting material to discuss CAP NI margin comment	

26-Sep-07	A	Response/Comments	Request telecom to discuss lack of PORT score II subjects in 11 SEP 07 comments	
26-Sep-07a	A	General	Status of meeting materials	
01-Oct-07	A	General	Status of meeting time to discuss PORT score II	
05-Oct-07	A	General	Status of cSSSI SAP review	
09-Oct-07	A	General	Division feels nothing further to discuss regarding CAP NI margin and PORT score II	
11-Oct-07	A	General	Status of Pediatric plan review	
15-Oct-07	A	General	Teleconference (02 NOV 07) to discuss CAP NI margin and PORT score II	
30-Oct-07	A	General	Re-submit #140 meeting material for 02 NOV 07 teleconference	
30-Oct-07a	A	General	Meeting logistics for 02 NOV 07 teleconference	
02-Nov-07	A	General	Re-submit #132 as this submission could not be located at Division	
02-Nov-07a	A	General	Cerexa posed questions and our expected responses	
02-Nov-07b	A	General	Informing Division that call is activated as they had not called in yet	
02-Nov-07c	A	Meeting Minutes	Executive Summary, type A telecon for CAP (PORT score, NI margin, SPA) (internal minutes - not submitted to FDA)	
13-Nov-07	A	General	Requesting advice on next steps for CAP studies (attachment: refer to 15 Mar 07 FDA letter)	
14-Nov-07	A	General	Will address concern regarding CAP studies with Dr. Chambers. FDA 02 NOV 07 meeting attendee list	
14-Nov-07a	A	General	SPA questions	
20-Nov-07	A	General	Request status of Pediatric plan review	
26-Nov-07	A	General	Pediatric plan review still pending	
26-Nov-07a	A	General	Clarification of meeting attendee: Joseph Toerner	
02-Jan-08	A	General	Requesting status of neeting minutes from the Type A telecon on 02 November 2008	P903-08, P903-09
03-Jan-08	A	Safety	Email notifying late safety report for P903-09 (serial#163)	P903-09
15-Jan-08	A	Response_comments	Requesting additional comments on P903-05 QTc study	P903-05
29-Jan-08	A	Response_comments	P903-05 can move forward	P903-05
06-Feb-08	A	General	Question regarding ClinicalTrials.gov and Form FDA 3674	
12-Feb-08	A	General	Question regarding stage of protocol that should be submitted if submitting under a Special Protocol Assessment (SAP)	P903-08, P903-09

12-Feb-08a	A	Safety	7-day alert reported to FDA-CRXA2007000097	P903-09
13-Feb-08	A	General	FDA request timing of the Ceftaroline NDA filing	
17-Mar-08	A	Response/Comments	Cerexa submitted questions regarding a proposed Phase 3 study in nosocomial pneumonia and received FDA comments. Question posed by Cerexa include 1) since Cerexa is doing two phase 3 studies in CAP, would a single NP study be adequate and 2) is our proposed primary outcome measures acceptabled	P903-10?
01-Apr-08	A	General	Cerexa would like to submit a Type C meeting for HAP/NP and would like to know if it is acceptable for Cerexa to discuss FDA's informal feedback (17Mar08) in the meeting package.	P903-10?
01-Apr-08a	A	General	Chemists comments on the Annual Report. Requesting DMF number for ABL once it is available.	Annual Report
16-May-08	A	Safety	7-day alert reported to FDA-CRXA2008000150	P903-09
20-May-08	A	General	Request meeting minutes from the 02 Novemeber Type A Teleconference regarding Cerexa's CAP studies	P903-08, P903-09
21-May-08	A	General	Informed Carmen that we have not received the meeting minutes for the 02 November 2007 Type A teleconference	P903-08, P903-09
28-May-08	A	Safety	7-day alert reported to FDA-CRXA2008000156	P903-08
28-May-08a	A	General	Informed Carmen D. that we did not receive comments on the Skin SAP submitted in October (Serial # 129) and that we will be submitting an Amendment	P903-06, P903-07
18-Jun-08	A	General	P903-06 and P903-07; Emailed Carmen DeBellas the Phase 3 cSSSI Press Release	P903-06, P903-07
19-Jun-08	B	General	Call Carmen about Press Release	P903-06, P903-07
3-Jul-08	B	Safety	7-day safety for P903-08 CRXA2008000179 subject 2034-08238/AJC Unknown Sudden Death [Sudden death]	P903-08
7-Jul-08	B	General	Request for 02-Nov-07 Type A Meeting Minutes	P903-08, P903-09
10-Jul-08	B	General	Request status of 02-Nov-07 Type A Meeting Minutes	P903-08, P903-09
22-Jul-08	B	Safety	7-day safety report	P903-08
28-Jul-08	B	General	Email response to FDA's inquiry of when we plan to submit the NDA for ceftaroline.	

21-Aug-08	B	General	Request status of 02-Nov-07 Type A Meeting Minutes	P903-08, P903-09
17-Sep-08	B	General	Ensuring communication with the FDA has only occurred with Cerexa and not Forest	
19-Sep-08	B	Meeting Minutes	FDA meeting minutes from November 2, 2007 Type A meeting.	P903-08, P903-09
19-Sep-2008a	B	Meeting Minutes	Official copy of minutes from Nov. 2, 2007 Type A meeting (mailed).	P903-08, P903-09
25-Sep-08	B	General	Placement of ISS and ISE in eCTD	eCTD
26-Sep-08	B	General	1) Status of P-903-15 protocol amendment, 2) Submission of P903-05 SAP, and 3) Status of ISS/ISE placement in eCTD response.	P903-15, P903-05 and eCTD
1-Oct-08	B	General	Carmen DeBellas requested submission numbers. Cerexa response of outstanding items.	P903-15
7-Oct-08	B	Response/Comments	FDA response on the placement of the ISS/ISE in the eCTD	
15-Oct-08	B	General	P903-15 Notifying FDA that we are implementing amendment to protocol	P903-15
20-Nov-08	B	Safety	7-Day Safety Report	P903-08
8-Jan-09	B	Response_Comments	FDA comments on P903-08 and P903-09 SAP amendment 1 (re. SN264 and 265)	P903-08, P903-09
12-Jan-09	B	General	Enquiring about separate CMC Type B meeting. New contact Jeannie David, CMC project manager	N/A
13-Jan-09	B	General	Email to Carmen DeBellas inquiring if Cerexa should expect comments on the cSSSI SAP.	P903-06, P903-07
22-Jan-09	B	General	Providing Digital ECG Data to the ECG warehouse	P903-05
3-Feb-09	B	General	Cerexa-RA contacted Carmen DeBellas to ask for clarification regarding the request for pre-NDA process.	N/A
05-Feb-09	B	General	Cerexa contacted Carmen DeBelllas regarding placement and submission of microbiology reports	N/A
17-Feb-09	B	Safety	Cerexa contacted Carmen DeBelllas re. a 7-Day Safety Report	P903-19
24-Feb-09	B	General	Status of P903-06 and P903-07 SAP Reviewers Comments	P903-06, P903-07
24-Mar-09	B	General	New Guidance for CAP	
31-Mar-09	B	General	cSSSI SAP Comments. Acknowledge receipt of change of address status of pre-NDA meeting letter.	
31-Mar-09	B	FDA Letter	meeting granted for Type B clinical /nonclinical preNDA	N/A
7-Apr-09	B	General	CMA pre-NDA meeting request protocol - eCTD	preNDA

9-Apr-09	B	Response_Comments	FDA comments on cSSSI SAP	P903-06, P903-07
10-Apr-09	B	General	Clarification on the Type B meeting information and request for acknowledgment of receipt of cSSSI SAP	preNDA, P903-06, P903-07
10-Apr-09 a	B	General	acknowledgment of receipt of cSSSI SAP	P903-06, P903-07
13-Apr-09	B	General	requesting information on the CMC preNDA and project manager	preNDA
14-Apr-09	B	General	confirming receipt of P903-05 SAP amendment and realizing submission numbering between FDA and Cerexa not matching	P903-05
14-Apr-09 a	B	General	Called Carmen D. about problems with serial number not matching	
16-Apr-09	B	General	problems with the CSR submission and subsequent resolution	P903-02, P903-03, P903-13, P903-17
17-Apr-09	B	General	Contact information for Jeanie David, CMC PM, information on obtaining secure electronic mail exchange and acknowledgment of CMC preNDA meeting request	preNDA
22-Apr-09	B	General	acknowledgment of receipt of CMC Type B meeting request	preNDA
29-Apr-09		FDA Letter	Time change for the nonclinical/clinical preNDA meeting in July 7, 2009	preNDA
4-May-09		General	Contact C. DeBellas on CMC preNDA meeting request	preNDA
6-May-09	B	FDA Letter	Request for IND #	
7-May-09	B	FDA Letter	Information on the CMC preNDA meeting. Meeting granted by phone and dates determine	preNDA
15-May-09	B	FDA Letter	DMF no. 11321 Type III	
26-May-09	B	General	Confirmation of receipt of cSSI SAP response Studies: P903-06/P903-07	P903-06, P903-07
5-Jun-09	B	General	Request for a list of Division attendees to the Type C Pre-NDA CMC meeting.	preNDA
8-Jun-09	B	General	PreNDA meeting logistics - foreign visitor	preNDA
08-Jun-09 a	B	General	PreNDA meeting request - copy of questions in word	preNDA
17-Jun-09	B	General	ROC regarding: 1) date of pre-meeting, 2) submission of revised ISS outline	preNDA
19-Jun-09	B	General	D. Friedland's foreign visitor form for pre-NDA meeting	preNDA
24-Jun-09	B	General	Nonclinical/Clinical Pre-NDA: confirm email receipts and clarification on 17Jun09 call regarding pre-NDA response.	preNDA

25-Jun-09	B	General	Request for CXL IND - CD copies	CXL IND
26-Jun-09	B	Response & Comments	FDA response to preNDA microbiology questions.	
29-Jul-09	B	General	PreNDA meeting logistics	preNDA
1-Jul-09	B	FDA Letter	PreNDA Type B CMC Meeting	preNDA
01-Jul-09 a	B	FDA Letter	IND 71, 371 submission 30 Jul 09 SSN340	
01-Jul-09 b	B	FDA Letter	CMC meeting date schedule for July 22, 09	preNDA
2-Jul-09	B	Response & Comments	Pre-NDA meeting comments for Tuesday (IND 71, 371)	preNDA
6-Jul-09	B	General	Pre-NDA meeting - Cerexa/Forest attendee list change.	preNDA
7-Jul-09	B	General	Quality Assessment for NDA/BLA Submission checklist - provided by FDA PM prior to Pre-NDA meeting.	preNDA
13-Jul-09	B	Response & Comments	Pre-NDA meeting - FDA Response to Revised ISS Outline	preNDA
15-Jul-09	B	General	Pre-NDA meeting - FDA Attendee List	preNDA
16-Jul-09	B	General	Pre-NDA meeting - Cerexa/Forest attendee list.	preNDA
20-Jul-09	B	Response & Comments	Pre-NDA Type B CMC Meeting - FDA Preliminary Responses	preNDA
30-Jul-09	B	Meeting Minutes	CMC PreNDA Meeeting Minutes 073009.doc	preNDA
31-Jul-09	B	Response & Comments	Draft Guidance for Industry-Acquired Bacterial Pneumonia Dev Drugs for Treatment	preNDA
5-Aug-09	B	General	FU to PreNDA: status of metabolite profiling report review and notification that the Cerexa meeting minutes were submitted.	preNDA
10-Aug-09	B	Response & Comments	Missing tables for submission #349 (Juvenile, 4- and 13-week data tables)	CPT-TX-03
21-Aug-09	B	Meeting Minutes	CMC PreNDA Meeeting Minutes (FDA Minutes)	CMC pre-NDA
20-Aug-09		Response & Comments	FDA response to Metabolite Profile report (submission 341, 14 Jul 09)	clinical P903-13 nonclinical PRD-RPT-BDM-00201
31-Aug-09		Response & Comments	Random subject numbers from Phase 3 studies (see submission dated 20 Jul 09)	
31-Aug-09 a		General	Cerexa request the status of PreNDA clinical/nonclinical meeting minutes and prefered way of obtaining NDA number	
1-Sep-09		General	Pre-Assigned NDA number (200327)	
2-Sep-09		Response & Comments	Clarification on random subject numbers from Phase 3 studies	
9-Sep-09		General	FDA requesting status of Cerexa's response to FDA's comments on the Metabolite Profile report	

17-Sep-09		General	Cerexa request receipt of the PPSR and clarification on the 120day review cycle. FDA confirms receipt of the PPSR.	
23-Sep-09		General	Request/response on status of nonclin/clin PreNDA meeting minutes	
28-Sep-09		General	Request a meeting with Carmen DeBellas to introduce Bruce Lu and discuss upcoming NDA	
28-Sep-09 a		General	email to Martara: Question to ECG warehouse - separate request for multiple protocols	
5-Oct-09		General	Introduce Bruce Lu and questions on upcoming filing (ECG uploads, raw datasets in CDISC, ISS lab dataset, PPSR, PreNDA mm, metabolite report response, starting material response, upcoming submission, review team)	
05-Oct-09 a		General	lab dataset for ISS - requesting for partitioning information	
6-Oct-09		Response & Comments	FDA response to lab dataset partitioning. Cerexa question regarding file size for datasets	
06-Oct-09 a		General	email to Martara: ECG warehouse - timing of uploads	
7-Oct-09		General	FDA response to file size - esub information provided	
08-Oct-09		General	ECG warehouse - timing of uploads	
09-Oct-09		General	email to esub and FDA regarding file size and partitioning of lab dataset for ISS	
13-Oct-09		General	Question on Module 2 clinical summary document size. Question on the placement of the Microbiological data.	
20-Oct-09		Response & Comments	Question from FDA and Cerexa response on the dataset partitioning. Including additional questions on datasets.	
21-Oct-09		Meeting Minutes	July 7, 2009 preNDA nonclinical/clinical meeting minutes (official FDA minutes)	preNDA
28-Oct-09		General	FDA called stating they have not received the dataset submission dated 09Oct09 (Serial No. 358). Called Carmen D. to ensure he received the CD for the sample datasets. Also, requested if he had time to discuss the Cerexa response to the Metabolic Report	
30-Oct-09		General	IRT wanted to know if they could start reviewing P903-05 (submitted 12Oct09). Cerexa responded yes.	P903-05

29-Oct-09		General	FDA confirmed they received the sample dataset DVD (submitted 28Oct09). Cerexa request when we should expect comments on sample datasets, metabolite report response and starting material justification.	NDA
2-Nov-09		General	FDA respond to the status of the metabolite report response and starting material justification.	preNDA fu
6-Nov-09		Response & Comments	FDA respond to submission dated 9/30/09: Metabolic Profiling Response and P903-13 Mass Balance Response.	
12-Nov-09		General	Expected date for the starting material justification response	preNDA fu
2-Dec-09		Response & Comments	FDA provided comments on the sample dataset for P903-06 (Serial # 0361)	preNDA fu
4-Dec-09		General	Planning Telecom to discuss sample dataset	preNDA fu
7-Dec-09		General	List of FDA attendees for 11Dec09 telecon to discuss sample dataset comments	preNDA fu
7-Dec-09		Response & Comments	Cerexa response to FDA comments on sample dataset (correspondence 02Dec09) Later replaced with response sent 09Dec09	preNDA fu
9-Dec-09		Response & Comments	Cerexa final response to FDA comments on sample dataset (correspondence 02Dec09)	preNDA fu
11-Dec-09		General	List of Cerexa attendees	preNDA fu
15-Dec-09		General	Confirm NDA number with CDER	NDA
16-Dec-09		Response & Comments	Data set response/comments and meeting minutes from Dec 11, 2009 telecon with the FDA.	preNDA fu
5-Jan-10		General	ECG warehouse notification for P903-05	P903-05
5-Jan-10 a		FDA Letter	Letter that PPSR not adequate for written request "INADEQUATE STUDY REQUEST"	
20-Jan-10		General	Follow up regarding the starting material response. Jeannie David responsible for this task.	
27-Jan-10		General	Proposed plan to handle pediatric assessment and PPSR response.	
29-Jan-10		General	Followup with FDA on Proposed plan to handle pediatric assessment and PPSR response.	
2-Feb-10		General	Requested status on proposed plan to handle pediatric assessment and PPSR response. Carmen to check with Reviewers.	

2-Feb-10a		Response & Comments	Reviewers comment on proposed plan to handle pediatric assessment and PPSR response.	

IND SUBMISSION LOG

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
01-Nov-10		372		Other: Transfer of Regulatory Obligation	Pharmacokinetics of Single Dose of CPT in Children Birth to younger than 12 with suspected or confirmed systemic infection.	P903-21
26-Oct-10		371		Information Amendment(s): Clinical	Updated version of IB and corresponding SOC.	
28-Sep-10		370		Protocol Amendment(s): New Protocol	New protocol attachment, Fm1571 and CV	P903-21
12-Jun-10		369		Information Amendment(s): Clinical	Form 1571	P903-09
22-Jun-10		368		Information Amendment(s): Clinical	Form 1571 and Updated version of Investigator's Brochure; edition 10, supercedes ed. 9	
12-May-10		367		Information Amendment(s): Pharmacology/Toxicology	Attachment 1: CEF-TX-10, Attachment 2: CEF-TX-14, and Attachment 3: P0903-T-040	PPI-0903
11-Mar-10		366		Annual Report	FDA Form 1571, Annual Report, CMC Attachment, P903-08,09, and 19 Synopses	
10-Feb-10		365		Protocol Amendment(s): New Investigator	FM FDA 1572 and CV	P903-06
02-Feb-10		364		Informational Amendment(s): Clinical	Response to FDA Inadequate Study Request letter dated 05Jan2010. SN350 PPSR.	
29-Jan-10		363		Protocol Amendment(s): New Investigator	FM FDA 1572 and CV	
09-Dec-09		362		Information Amendement(s): Clinical Response to FDA Request for Information	Attachment 1: Ceftaroline Info Request & Comments Re. The Sample Datasets for Study P903-06	P903-06

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
27-Oct-09		361		Information Amendment(s): Clinical Response to FDA Request for Information	Fm 1571, Cover Letter and DVD of sample raw dataset (copy also sent to PM)	dupe of SN358
16-Oct-09		360		Information Amendment(s): Chemistry & Microbiology	FM1571, Cover Letter and Attach1:P0903-M-026, Attach2:P0903-M-039, Attach2:P903-M-062, and Attach4:P903-M-082	P903-08 and P903-09
12-Oct-09		359		Information Amendment(s): Clinical	Final Clinical Study Report (4 volumes)	P903-05
09-Oct-09		358		Information Amendment(s): Clinical Response to FDA Request for Information	Fm 1571, Cover Letter and DVD of sample raw dataset	P903-06
02-Oct-09		357		Response to FDA Request for CMC information	22Jul09 Type B, pre-NDA CMC Teleconference minutes Reg. Starting Materials	PPI-0903
30-Sep-09		356		General Correspondence	Response to Division comments on Metabolite Profile report PRD-RPT-BDM-00201 (submission 0341), 20 August 2009	P903-13
11-Sep-09		355		Protocol Amendment(s): Chemistry & Microbiology	Non-clinical study reports P0903-M-041, P903-M-058, P903-M-059, P903-M-060, P903-M-061, P903-M-069, P903-M-070, P903-M-072, P903-M-076, P903-M-84, P903-M-085	
03-Sep-09		354		Protocol Amendment(s): Pharmacology/Toxicology	Final non-clinical study reports: CEF-TX-01, CEF-TX-02	
03-Sep-09		353		Protocol Amendment(s): Chemistry & Microbiology	Final non-clinical study report: P0903-M-023, P0903-M-043, P0903-M-044	
20-Aug-09		352		Protocol Amendment(s): New Investigators	New Investigator 1572 and CV	P903-08
12-Aug-09		351		Information Amendment(s): Clinical - Clinical Study Report, P903-20	FM 1571 and Cover; CSR	P903-20

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
10-Aug-09		350		Other: Proposed Pediatric Study Request	Copy of PPSR	
05-Aug-09		349		Protocol Amendment(s): Pharmacology/Toxicology	CPT-TX-03 Juvenile toxicology study (tables referenced in cover letter was provided via email to PM on 10 Aug 09)	CPT-TX-03 or CEF-TX-03
31-Jul-09		348		General Correspondence: Cerexa Meeting Minutes for Type B Pre-NDA Meeting	Cerexa's meeting minutes from PreNDA nonclinical/clinical meeting	
29-Jul-09		347		Protocol Amendment(s): New Investigator	Revised Forms FDA-1572	P903-08
29-Jul-09		346		Protocol Amendment(s): New Investigator	Revised Forms FDA-1572	P903-09
20-Jul-09		345		Protocol Amendment(s): Response to FDA Request for Information	CD of subject ID numbers, four files; one study per file plus hard copy.	P903-06, P903-07, P903-08, P903-09
17-Jul-09		344		IND Amendment(s):Pharmacology/Toxicology	CEF-TX-11 Final Report Two Volumes	
17-Jul-09		343		IND Amendment(s): Clinical	Fm 1571 and Cover Letter	P903-11
16-Jul-09		342		IND Amendment(s): Clinical	Fm 1571 and Cover Letter	P903-18
14-Jul-09		341		IND Amendment(s):Pharmacology/Toxicology	PRD-RPT-BDM-00201 Metabolite Profile Report (sample from P903-13)	P903-13
30-Jun-09		340		IND Amendment(s): Clinical	P903-08 and P903-09 Draft Synopsis	P903-08 P903-09
29-Jun-09		339		IND Safety Report(s): Follow-up to a Written Report	FDA Form 3500A that contains 15-day follow-up. CRXA2008000177, PI 8203-08218/OBE; CRXA2008000179, PI 2034-08238/AJC; CRXA2008000190, PI 2029-08223/R-T;CRXA2008000196, PI 2029-08266/NMA; CRXA2008000236, PI 6641-08578/G-Z	P903-08

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
23-Jun-09		338		Information Amendment: Chemistry/Microbiology	Non-clinical study report P0903-M-053	
19-Jun-09		337		Protocol Amendment(s): New Investigator	Revised Forms FDA-1572	P903-09
19-Jun-09		336		Protocol Amendment(s): New Investigator	Revised Forms FDA-1572	P903-08
17-Jun-09		335		Other: Correction to Type B Pre-NDA Meeting Briefing Book	Correction and attachment: Rev. ISS outline for Appendix VIII of 01 June 09 Briefing Book	
15-Jun-09		334		IND Safety Report(s): Follow-up to a Written Report	Mfr. Report CRXA2008000097. Patient No. 6509-09273EWV; 15-day follow-up #6 information	P903-09
15-Jun-09		333		IND Safety Report(s): Follow-up to a Written Report	Mfr. Report CRXA2007000075. Patient No. 3005-09131 / SCC; 15-day follow-up #5 information.	P903-09
15-Jun-09		332		Protocol Amendment(s): Change in Protocol	Amendments for studies P903-08 and P-903-09 and corresponding SOCs.	P903-08, P903-09
12-Jun-09		331		Information Amendment: Chemistry/Microbiology	Twelve final non-clinical study reports: P0903-M-024, P0903-M-035, P0903-M-036, P0903-M-038, P0903-M-040, P-0903-M-043, P0903-M-044, P0903-M-045, P0903-M-050, P0903-M-054, P0903-M-055, P0903-M-057.	
12-Jun-09		330		Information Amendment: Phamacology/Toxicology	Final non-clinical study report: P903-T-016	
10-Jun-09		329		Information Amendment: Chemistry/Microbiology	COA's, Stability Data.	
11-Jun-09		328		Other: Briefing Book for Type B Pre-NDA CMC Meeting.	20 additional copies to Jeannie David	
09-Jun-09		327		Information Amendment: Phamacology/Toxicology	Toxicology Study No. 1281-010 (CF-TX-11)	
04-Jun-09		326		Information Amendment: Phamacology/Toxicology	Four final non-clinical study reports: CEF-PK-01-(xt083061), P903-P-006, P903-P-007, and P903-P-008.	

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
01-Jun-09		325		This file contains Cover Letter and Fm 1571 of SN 324	Pre-NDA meeting Briefing Book for July 7, 2009 meeting (20 additional copies to Carmen DeBellas)	Dupe of SN324
01-Jun-09		324		Type B Pre-NDA Meeting Briefing Book	Pre-NDA Meeting Request, 25 March 2009 (Serial Number 290) and Division's confirmation of meeting, 31 March 2009 and 29 April 2009	
27-May-09		323		Information Amendment: Clinical	Clinical Study Reports - P903-04 (Mailed Form 1571 and Cover letter to Wendy Gill)	P903-04
22-May-09		322		Protocol Amendment: New Investigator	Revised Forms FDA-1572	P903-09
22-May-09		321		Protocol Amendment: New Investigator	Revised Forms FDA-1572	P903-08
22-May-09		320		Information Amendment: Clinical	Statistical Analyst Plan Amendments (SAP), Studies P903-08 and P903-09	P903-08/09
15-May-09		319		Other: Response to Division comments re P903-06/07 SAPs	Response to Division comments re Study P903-06 and P903-07 Statistical Analysis Plans	P903-06/07
04-May-09		318		IND Safety Report(s): Follow-up to a Written Report	Mfr. Report CRXA2008000156. Patient No. 6626-08148 W-L. 15-day follow-up #6 information.	P903-08
01-May-09		317		Protocol Amendment(s): New Investigator	New Investigators, 1572, and CV	P903-15
01-May-09		316		Protocol Amendment(s): New Investigators	New Investigators, 1572, and CV	P903-08
29-Apr-09		315		IND Safety Report(s): Follow-up to a Written Report	15-day CRXA2008000156 follow-up #5. subject 6626-08148	P903-08
27-Apr-09		314		Annual Report	Ceftaroline fosamil annual report from January 13, 2008 to January 12, 2009 - Includes Investigator Brochure edition 9	
23-Apr-09		313		IND Safety Report(s): Follow-up to a Written Report	15-day CRXA2008000179 Patient No. 2034-08238/AJC 15-day Follow-up #5.	P903-08

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
16-Apr-09		312		Other: type B Pre-NDA Meeting Request	Type B Pre-NDA Meeting Request CMC only	
13-Apr-09	297	311		Other: Clinical Study Reports	Clinical Study Reports: P903-02, P903-03, P903-13, P903-17	P903-02, P903-03, P903-13, P903-17
10-Apr-09	296	310		Other: Statistical Analysis Plan: P903-05	P903-05 SAP Amendment 1 with SOC	P903-05
Note: Submissions after April 10, 2009 will need to start with Serial Number 312 to match numbering system of the FDA. Any submission inquiries to the FDA prior to April 10, 2009 must be done by submission date.						
08-Apr-09	295			IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000141. Patient No. 0039-19006 / AAJ 15-day follow-up 4	P903-19
02-Apr-09	294			General Correspondence	Contact Change to Steffangy Gaffagan and Trisha Dobson	N/A
27-Mar-09	293			Protocol Amendment(s): New Investigator	New Investigators, 1572, and CV	P903-08
27-Mar-09	292			Protocol Amendment(s): New Investigator	New Investigators, 1572, and CV	P903-09
27-Mar-09	291			Protocol Amendment(s): New Investigator	New Investigators, 1572, and CV	P903-08
25-Mar-09	290			Other: Type B Pre-NDA Meeting Request	Type B Pre-NDA Meeting Request. Excluding CMC	N/A
25-Mar-09	289			IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000141. Patient No. 0039-19006 / AAJ 15-day follow-up.	P903-19
19-Mar-09	288		63	Other: Address Change	Other: Address Change	
05-Mar-09	287		62	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000141. Patient No. 0039-19006 / AAJ 15-day initial information.	P903-19
24-Feb-09	286		62	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000141. Patient No. 0039-19006 / AAJ 15-day Follow-up #1 information.	P903-19

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
24-Feb-09	285		62	Other: Response to Division Comments	Response to Division Comments on Dated 08 January 2009 on the CABP SAP	P903-08 P903-09
20-Feb-09	284		62	Protocol Amendment(s): New Investigator	New Investigators, 1572, and CV	P903-09
20-Feb-09	283		62	Protocol Amendment(s): New Investigator	New Investigators, 1572, and CV	P903-08
17-Feb-09	282		62	IND Safety Report(s): Initial Written Report	Mfr. Report #CRXA2008000141. Patient No. 0039-19006 / AAJ 7-day initial information.	P903-19
06-Feb-09	281		62	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000236. Patient No. 6641-08578 G-Z. 15-day Follow-up #6 information	P903-08
06-Feb-09	280		62	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000236. Patient No. 6641-08578 G-Z. 15-day Follow-up #5 information	P903-08
28-Jan-09	279		62	Protocol Amendment(s): New Investigator	New Investigators, 1572, and CV	P903-15
28-Jan-09	278		62	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000236. Patient No. 6641-08578 G-Z. 15-day Follow-up #4 information	P903-08
20-Jan-09	277		62	Protocol Amendment(s): New Investigator	New Investigators, 1572, and CV	P903-09
20-Jan-09	276		62	Protocol Amendment(s): New Investigator	New Investigators, 1572, and CV	P903-08
07-Jan-09	275		62	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000236. Patient No. 6641-08578 G-Z. 15-day Follow-up #3 information	P903-08
22-Dec-08	274		62	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000236. Patient No. 6641-08578 G-Z. 15-day Follow-up #2 information	P903-08
18-Dec-08	273		62	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000236. Patient No. 6641-08578 G-Z. 15-day Follow-up #1 information	P903-08

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
18-Dec-08	272		61	Protocol Amendment(s): New Investigator	New Investigators, 1572, and CV	P903-09
18-Dec-08	271		61	Protocol Amendment(s): New Investigator	New Investigators, 1572, and CV	P903-08
25-Nov-08	270		61	Other: Revised Form FDA 1572	P903-19 Principal Investigator's with Revised Form 1572	P903-19
20-Nov-08	269		61	Protocol Amendment(s): New Investigator	New Investigators, 1572, and CV	P903-20
20-Nov-08	268		61	IND Safety Report(s): Initial Written Report	Mfr. Report #CRXA2008000236. Patient No. 6641-08578 G-Z 7-day Initial information	P-903-08
20-Nov-08	267		61	Protocol Amendment(s): New Investigator	New Investigators, 1572, and CV	P-903-08
07-Nov-08	266		61	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000156. Patient No. 6626-08148 W-L. 15-day Follow-up #4 information	P-903-08
28-Oct-08	265		61	Protocol Amendment(s): Change in Protocol	Amendment 3 of Protocol P903-09/corresponding SOC and Statistical Analysis Plan (SAP)	P903-09
28-Oct-08	264		61	Protocol Amendment(s): Change in Protocol	Amendment 3 of Protocol P903-08/corresponding SOC and Statistical Analysis Plan (SAP)	P903-08
22-Oct-08	263		60	Information Amendment(s): Chemistry/Microbiology	Non-clinical study report P0903-M-030	P0903-M-030
20-Oct-08	262		60	Protocol Amendment(s): New Investigator	New Investigators, 1572, and CV	P903-09
20-Oct-08	261		60	Protocol Amendment(s): New Investigator	New Investigators, 1572, and CV	P903-08
10-Oct-08	260		60	Other: Statistical Analysis Plan for Study P903-05	Provides the Statistical Analysis Plan (SAP)	P903-05
08-Oct-08	259		60	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000190. Patient No. 2029-08223/R-T 15-day Follow-up #3 information.	P903-08

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
01-Oct-08	258		60	Information Amendment(s): Chemistry/Microbiology	USAN & INN name and structure for Ceftaroline	
01-Oct-08	257		60	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000156. Patient No. 6626-08148 W-L. 15-day Follow-up #3 information	P903-08
01-Oct-08	256		60	Other: Supplement to Statistical Analysis Plan: P903-06/-07	SAP Suppliment: Additional analysis on hypersensitivity reaction	P903-06, P903-07
24-Sep-08	255		60	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000196. Patient No. 2029-08266/NMA 15-day Follow-up #5 information.	P903-08
24-Sep-08	254		60	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000190. Patient No. 2029-08223/R-T 15-day Follow-up #2 information.	P903-08
22-Sep-08	253		60	Protocol Amendment(s): New Investigator	New Investigator, 1572, and CV	P903-04
22-Sep-08	252		60	Protocol Amendment(s): New Investigator	New Investigator, 1572, and CV	P903-09
16-Sep-08	251		60	Protocol Amendment(s): Change in Protocol	P903-15 Protocol Amendment 2 and corresponding SOC	P903-15
12-Sep-08	250		60	Protocol Amendment(s): Change in Protocol	Amendment 3 version 2 of Protocol P903-09 and corresponding SOC. (Changes to format only).	P903-09
11-Sep-08	249		59	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000196. Patient No. 2029-08266/NMA 15-day Follow-up #4 information.	P903-08
04-Sep-08	248		59	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000172. Patient No. 6608-09527 W-G 15-day Follow-up #1 information	P903-09
28-Aug-08	247		59	Protocol Amendment(s): Change in Protocol	Amendment 3 version 1 of Protocol P903-09 and corresponding SOC	P903-09
27-Aug-08	246		59	Other: Statistical Analysis Plan for Study P903-09	Provides the Statistical Analysis Plan (SAP)	P903-09

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
27-Aug-08	245		59	IND Safety Report(s): Follow-up to a Written Report	Mfr Report#: CRXA2007000075, Patient #: 3005-09131/SCC 15-day Follow-up #4 information.	P903-09
22-Aug-08	244		59	Other: Revised Form FDA-1572	Revised Form FDA-1572	P903-06
20-Aug-08	243		59	Protocol Amendment(s): New Investigator	New Investigator, 1572, and CV	P903-04
20-Aug-08	242		59	Information Amendment(s): Chemistry/Microbiology	Nonclinical study report P0903-M-019, P0903-M-028	P0903-M-019 & P0903-M-028
20-Aug-08	241		59	Protocol Amendment(s): New Investigator	New Investigator, 1572, and CV	P903-08
20-Aug-08	240		59	Protocol Amendment(s): New Investigator	New Investigator, 1572, and CV	P903-09
19-Aug-08	239		59	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000179. Patient No. 2034-08238/AJC 15-day Follow-up #4 information	P903-08
19-Aug-08	238		59	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000177. Patient No. 8203-08218 / OBE. 15-day Follow-up #2 information.	P903-08
14-Aug-08	237		59	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000196. Patient No. 2029-08266/NMA 15-day Follow-up #3 information.	P903-08
06-Aug-08	236		59	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000196. Patient No. 2029-08266/NMA 15-day Follow-up #2 information.	P903-08
06-Aug-08	235		59	IND Safety Report(s): Initial Written Report	Mfr. Report #CRXA2008000172. Patient No. 6608-09527 W-G 15-day Initial information	P903-09
06-Aug-08	234		59	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000179. Patient No. 2034-08238/AJC 15-day Follow-up #3 information	P903-08

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
28-Jul-08	233		59	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000196. Patient No. 2029-08266/NMA 15-day Follow-up #1	P903-08
28-Jul-08	232		59	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000182. Patient No. 5230-08228 / GKD. 15-day Follow-up #2 information	P903-08
23-Jul-08	231		59	IND Safety Report(s): Initial Written Report	Mfr. Report #CRXA2008000196. Patient No. 2029-08266/NMA 7-day Initial information	P903-08
23-Jul-08	230		59	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000190. Patient No. 2029-08223/R-T 15-day Follow-up #1 information.	P903-08
23-Jul-08	229		59	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000177. Patient No. 8203-08218 / OBE. 15-day Follow-up #1 information.	P903-08
21-Jul-08	228		59	Protocol Amendment(s): New Investigator	New Investigator, 1572, and CV	P903-08
18-Jul-08	227		58	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000182. Patient No. 5230-08228 / GKD. 15-day Follow-up #1 information	P903-08
18-Jul-08	226		58	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000179. Patient No. 2034-08238 / AJC. 15-day Follow-up #2 information	P903-08
16-Jul-08	225			IND Safety Report(s): Initial Written Report	Mfr. Report #CRXA2008000182. Patient No. 5230-08228/GKD. 15-day Initial information. Intoxication anaemia [anaemia], Hyperbilirubinemia [hyperbilirubinaemia]	P903-08
16-Jul-08	224		58	IND Safety Report(s): Initial Written Report	Mfr. Report #CRXA2008000190. Patient No. 2029-08223/R-T 15-day Initial information, Acute chlecystitis [cholecystitis acute]	P903-08

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
11-Jul-08	223		58	IND Safety Report(s): Initial Written Report	Mfr. Report #CRXA2008000177. Patient No. 8203-08218 / OBE. 15-day Initial information.	P903-08
11-Jul-08	222		58	IND Safety Report(s): Follow-up to a Written Report	Mfr. Report #CRXA2008000179. Patient No. 2034-08238 / AJC. 15-day Follow-up #1 information	P903-08
03-Jul-08	221		58	IND Safety Report(s): Initial Written Report	Mfr. Report #CRXA2008000179. Patient No. 2034-08238 AJC, Unknown Sudden Death [Sudden Death]. 7-day Initial information.	P903-08
26-Jun-08	220		58	Protocol Amendment(s): Change in Protocol	Amendment 2 of Protocol P903-05 and corresponding SOC	P903-05
26-Jun-08	219		58	Protocol Amendment(s): New Investigator	New Investigator, 1572, and CV	P903-19
25-Jun-08	218		58	IND Safety Report: Follow-up To a Written Report	Follow-up on the following Patients/SAE#s: Mfr. Report #CRXA2007000003, Patient No. 0028-07002/TJB; Mfr. Report #CRXA2007000004, Pt. No. 2012-06611/S-S; Mfr. Report #CRXA2007000028, Pt. No. 0026-07208/WLM; Mfr. Report #CRXA2007000039, Pt. No. 2006-06444/AJB; Mfr. Report #CRXA2007000040, Pt. No. 6511-07312/D-K; Mfr. Report #CRXA2007000043, Pt. No. 6515-07368/IBA; Mfr. Report #CRXA2007000048, Pt. No. 5014-07467/NAR; Mfr. Report #CRXA2007000053, Pt. No. 2012-06611/MAB; Mfr. Report #CRXA2007000060, Pt. No. 3004-06679/JJB.	P903-06 and P903-07

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
20-Jun-08	217		58	IND Safety Report: Follow-up To a Written Report	Mfr. Report #CRXA2008000156. Patient No. 6626-08148 W-L. 15-day Follow-up #2 information	P903-08
20-Jun-08	216		58	Protocol Amendment(s): New Investigator	New Investigator, 1572, and CV	P903-09
20-Jun-08	215		58	Protocol Amendment(s): New Investigator	New Investigator, 1572, and CV	P903-08
06-Jun-08	214		57	IND Safety Report: Follow-up To a Written Report	Mfr. Report #CRXA2008000156. Patient No. 6626-08148. 15-day Follow-up #1 information	P903-08
03-Jun-08	213		57	Other: Statistical Plan P903-06/07	Update to SAP originally submitted on 08 Oct 2007. Submission included updated SAP and summary of changes.	P903-06 and P903-07
03-Jun-08	212		57	Protocol Amendment(s): New Investigator	New Investigator 1572 and CV	P903-15
30-May-08	211		57	IND Safety Report: Follow-up To a Written Report	Mfr. Report #CRXA2008000150. Patient No. 6613-09497. 15-day Follow-up #2	P903-09
28-May-08	210		57	IND Safety Report(s): Initial Written Report	Mfr. Report #CRXA2008000156. Patient No. 6626-08148. 7-day Initial information.	P903-08
23-May-08	209		57	IND Safety Report(s): Initial Written Report	Mfr. Report #CRXA2008000150. Patient #6613-09497/M-Z 15-day Follow-up#1	P903-09
21-May-08	208		57	Protocol Amendment(s): New Investigator	New Investigator, 1572, and CV	P903-19
21-May-08	207		57	Protocol Amendment(s): Change in Protocol and New Investigator	P903-05, Protocol Amendment 1 and corresponding SOC, New Investigator 1572 and CV, TOO, Medical Monitor CV: Ed Fang, MD	P903-05
20-May-08	206		56	Protocol Amendment(s): New Investigator	P903-09 New Investigator 1572 and CV and Principal Investigator's with Revised Form 1572	P903-09
20-May-08	205		56	Protocol Amendment(s): New Investigator	New Investigator 1572 and CV	P903-08

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16-May-08	204		56	IND Safety Report: Initial Written Report	Mfr Report# CRXA2008000150, Patient #6613-09497/M-Z, Lower limb ischemia/arterial thrombosis [Peripheral ischaemia] Arterial thrombosis [Arterial thrombosis limb], 7-day	P903-09
12-May-08	203		56	Information Amendment: Chemistry/Microbiology	Letter of Authorization from ABL with the DMF file number.	
08-May-08	202		56	Information Amendment: Chemistry/Microbiology	Phase 1, 2 and 3 Ceftaroline for Injection Lots used in clinical studies. Enclosed C of A	
02-May-08	201		56	Protocol Amendment(s): New Investigator	New Investigator 1572 and CV	P903-19
02-May-08	200		56	Protocol Amendment(s): New Investigator; Other: Transfer of Obligation	New Investigator 1572 and CV, TOO CRO	P903-09
02-May-08	199		56	Protocol Amendment(s): New Investigator; Other: Transfer of Obligation	New Investigator 1572 and CV, TOO CRO	P903-08
23-Apr-08	198		56	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2008000097, Patient #: 6509-09273, / JUI, Seizures [Convulsion], FU#5	P903-09
23-Apr-08	197		56	Information Amendment(s): Chemistry/Microbiology	Nonclinical study report P0903-M-025, P0903-M-029, P0903-M-033, P0903-M-034 and P0903-M-037	
09-Apr-08	196		56	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2008000097, Patient #: 6509-09273, / JUI, Seizures [Convulsion], FU#4	P903-09
28-Mar-08	195		56	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2008000097, Patient #: 6509-09273, / JUI, Seizures [Convulsion], FU#3	P903-09

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25-Mar-08	194		56	Information Amendment(s): Chemistry/Microbiology	Ceftaroline carton label and vial label for P903-06, P903-07, P903-08, P903-09	P903-06, P903-07, P903-08, P903-09
25-Mar-08	193		56	Protocol Amendment(s): Change in Protocol	P903-19, Protocol Amendment 1 and corresponding SOC	P903-19
25-Mar-08	192		56	Information Amendment(s): Chemistry/Microbiology	Ceftaroline carton label and vial label for P903-19	P903-19
21-Mar-08	191		55	Annual Report	Third Annual Report (Report Period: 13Jan07 through 12Jan08)	
21-Mar-08	190		55	Protocol Amendment(s): New Investigator; Other: Revised Form FDA-1572	P903-15 New Investigator 1572 and CV and Principal Investigator's with Revised Form 1572	P903-15
21-Mar-08	189		55	Protocol Amendment(s): New Investigator	New Investigator 1572 and CV	P903-08
20-Mar-08	188		55	Protocol Amendment(s): New Investigator; Other: Revised Form FDA-1572	P903-09 New Investigator 1572 and CV and Principal Investigator's with Revised Form 1572	P903-09
20-Mar-08	187		55	Protocol Amendment(s): New Investigator	New Investigator 1572 and CV	P903-19
19-Mar-08	186		55	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2008000097, Patient #: 6509-09273, / JUI, Seizures [Convulsion], FU#2	P903-09
04-Mar-08	185		55	Protocol Amendment(s): Change in Protocol	P903-04, Protocol Amendment 2 and corresponding SOC	P903-04
04-Mar-08	184		55	Information Amendment(s): Chemistry/Microbiology	Nonclinical Study Report P0903-M-021 and P0903-M-022	P0903-M-021 P0903-M-022
22-Feb-08	183		55	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2008000097, Patient #: 6509-09273, / JUI, Seizures [Convulsion], FU#1	P903-09

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
22-Feb-08	182		55	Protocol Amendment: New Investigator Other: Revised Form FDA-1572	P903-07 New Investigator 1572 and CV and Principal Investigator's with Revised Form 1572	P903-07
15-Feb-08	181		55	IND Safety Report(s): Initial Written Report	Mfr Report#: CRXA2008000097, Patient #: 6509-09273, / JUI, Seizures [Convulsion], 7-day (FDA called and emailed 02Feb08)	P903-09
14-Feb-08	180		55	Protocol Amendment(s): Change in Protocol	P903-15 Protocol Amendment 1 and corresponding SOC	P903-15
08-Feb-08	179		54	Protocol Amendment(s): New Protocol	P903-11 Elderly protocol Phase 1: New Investigator 1572 and CV, TOO of safety to Covance, Medical Monitor CV: Doug Rank, MD	P903-11
07-Feb-08	178		54	Protocol Amendment(s): New Protocol	P903-19 IM protocol Phase 2: New Investigator 1572 and CV, TOO of safety to Covance, Medical Monitor CV: Ed Fang, MD	P903-19
05-Feb-08	177		54	General Correspondence	The regulatory contact has been changed to Carmen Betancourt, MBA, Acting Head of Regulatory and Steffany Gaffagan, Manager of Regulatory Affairs.	
31-Jan-08	176		54	IND Safety Report: Follow-up To a Written Report	Mfr. Report No. CRXA2007000053, Patient # 2012-06611 / MAB, Blinded Hypersensitivity Reaction [Hypersensitivity], FU#6	P903-06
31-Jan-08	175		54	IND Safety Report: Follow-up To a Written Report	Mfr. Report No. CRXA2007000085, Patient # 7005-09055 / SMK, Blinded Interlobular pleurisy [Pleurisy], FU#3	P903-09
24-Jan-08	174		54	Other: Revised Form FDA-1572	P903-13 Principal Investigator's with Revised Form 1572	P903-13
24-Jan-08	173		54	Other: Revised Form FDA-1572	P903-09 Principal Investigator's with Revised Form 1572	P903-09
24-Jan-08	172		54	Protocol Amendment: New Investigator	New Investigator 1572 and CV	P903-09

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
24-Jan-08	171		54	Other: Revised Form FDA-1572	P903-04 Principal Investigator's with Revised Form 1572	P903-04
17-Jan-08	170		54	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2007000085, Patient #: 7005-09055/SMK, Interlobular pleurisy [Pleurisy], follow-up #2	P903-09
17-Jan-08	169		54	IND Safety Report: Follow-up to Written Report	Mfr Report#: CRXA2007000048, Patient #: 5014-07467/ NAR, Acute renal failure [Renal failure acute], Follow- up #4	P903-07
15-Jan-08	168		54	Information Amendment: Chemistry/Microbiology	CMC information for [14C] ceftaroline fosamil and [14C] ceftaroline drug product solution, info. to support P903-13 Mass Balance study	P903-13
15-Jan-08	167		54	Protocol Amendment: New Protocol	P903-13 Mass Balance protocol Phase 1: Change in Protocol - Amendment 1 and SOC, New Investigator 1572 and CV, TOO of safety to Covance, Medical Monitor CV: Doug Rank, MD	P903-13
14-Jan-08	166		54	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2007000075, Patient #: 3005-09131/SCC, Liver enzymes elevations [Hepatic enzyme abnormal], Follow up # 3, study closed	P903-09
07-Jan-08	165		54	IND Safety Report: Follow-up to Written Report	CRXA2007000054, Subject No. 2010-09032/ AVR, Pleural Effusion [pleural effusion], Follow- up #4	P903-09
07-Jan-08	164		54	IND Safety Report: Follow-up to Written Report	Mfr Report#: CRXA2007000048, Patient #: 5014-07467/ NAR, Acute renal failure [Renal failure acute], Follow- up #3	P903-07
03-Jan-08	163		54	IND Safety Report: Initial Written Report and Follow Up To a Written Report	Mfr Report#: CRXA2007000085, Patient #: 7005-09055/SMK, Interlobular pleurisy [Pleurisy], initial and follow-up #1	P903-09
03-Jan-08	162		54	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2007000075, Patient #: 3005-09131/SCC, Liver enzymes elevations [Hepatic enzyme abnormal], Follow up # 2	P903-09

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
21-Dec-07	161		53	Protocol Amendment: New Investigator	New Investigator 1572 and CV	P903-09
20-Dec-07	160		53	IND Safety Report: Follow-up To a Written Report	CRXA2007000054, Subject No. 2010-09032/ AVR, Pleural Effusion [pleural effusion], Follow- up #3	P903-09
19-Dec-07	159		53	Protocol Amendment: New Protocol	P903-08 CAP protocol Phase 3: Change in Protocol - Amendment 1 and 2, Protocol including New Investigator 1572 and CV, Medical Monitor CV: Paul Eckburg, MD	P903-08
19-Dec-07	158		53	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2007000075, Patient #: 3005-09131/SCC, Hepatitis [Hepatitis], Follow up # 1	P903-09
19-Dec-07	157		53	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2007000053, Patient #: 2012-06611/MAB, Hypersensitivity [Hypersensitivity], Follow up # 5, case closed	P903-06
06-Dec-07	156		53	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2007000053, Patient #: 2012-06611/MAB, Hypersensitivity [Hypersensitivity], Follow up # 4	P903-06
04-Dec-07	155		53	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2007000053, Patient #: 2012-06611/MAB, Hypersensitivity [Hypersensitivity], Follow up # 3	P903-06
29-Nov-07	154		53	IND Safety Report: Initial Written Report	Mfr Report#: CRXA2007000075, Patient #: 3005-09131/SCC, Hepatitis [Hepatitis]	P903-06
10-Dec-07	153			Protocol Amendment: New Protocol	P903-15 Pediatric protocol Phase 1: Protocol including New Investigator 1572 and CV, TOO of safety to Covance, Medical Monitor CV: Ed Fang, MD	P903-15
28-Nov-07	152		53	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2007000043, Patient #: 6515-07368/IBA, Anaphylactic shock, Follow up # 3	P903-06

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
26-Nov-07	151		53	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2007000004, Patient #: 0003-07006/SS, Anaphylactoid reaction, Follow up # 4, case closed	P903-06
26-Nov-07	150		53	Protocol Amendment: New Investigator	New Investigator 1572 and CV Transfer of Obligation to Covance Safety	P903-04
20–Nov-07	149		53	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2007000060, Patient #: 3004-06679/JJB, Diarrhea due to Clostridium difficile, Follow up # 2	P903-06
26-Nov-07	148		53	Protocol Amendment: New Investigator	New Investigator 1572 and CV	P903-09
16-Nov-07	147		53	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2007000039, Patient #: 2006-06444/AJB, Hypersensitivity Reaction, Follow up # 2	P903-06
16-Nov-07	146		53	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2007000040, Patient #: 6511-07312/D-K, Clinical Worsening of General Condiation, Follow up # 5	P903-07
13-Nov-07	145		53	IND Safety Report: Follow-up To a Written Report	Mfr Report#: CRXA2007000053, Patient #: 2012-06611/MAB, Hypersensitivity Reaction, Follow up # 2	P903-07
09-Nov-07	144		53	Information Amendment: Chemistry/Microbiology	Phase 1 domestic study label text: carton and vial	
06-Nov-07	143		52	Other: Protocol P903-05: Response to Division Comments dated 31 July 2007	Response to Division Comments on TET protocol dated 31 July 2007 received via email.	P903-05
07-Nov-07	142		52	IND Safety Report: Follow-Up to a Written Report P903-07	Mfr Report #: CRXA2007000028, Patient #: 0026-07208/WLM, Hypocoagulation, Follow up # 4, case closed	P903-07
05-Nov-07	141		52	Protocol Amendment: New Investigator	New Investigator 1572 and CV	P903-09
30-Oct-07	140		52	Other: Background and Questions for Telephone Call Scheduled on 02 November 2007	Background and Questions for 02 Nov 07 telecon regarding P903-08 and P903-09 Port Score and NI margin.	P903-08 P903-09
02-Nov-07	139		52	Protocol Amendment: New Investigators	New Investigator 1572 and CV	P903-06 P903-07

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
30-Oct-07	138		52	IND Safety Report: Follow-up to a Written Report	CRXA2007000040 Subject No. 6511-07312 / D-K Clinical worsening of general conditions [Condition aggravated] Follow-up #4	P903-07
24-Oct-07	137		52	IND Safety Report: Follow-up to Written Report	CRXA2007000060 Subject No. 3004-06679/ JJB Follow- up #1	P903-06
23-Oct-07	136		52	Other: Revised Form FDA-1572	P903-06 & P903-07 Principal Investigator's with Revised Form 1572	P903-06 P903-07
22-Oct-07	135		52	Protocol Amendment: New Protocol	P903-20 Protocol including New Investigator 1572 and CV & Medical Monitor CV: Doug Rank, MD, TOO to Covance safety	P903-20
19-Oct-07	134			IND Safety Report: Follow-up to Written Report	CRXA2007000028 Subject No. 0026-07208/ WLM Follow- up #3:	P903-07
17-Oct-07	133		52	IND Safety Report: Initial Written Report	CRXA2007000060 Subject No. 3004-06679/ JJB Event: Diarrhea due to Clostridium difficile [Clostridial infection]	P903-06
15-Oct-07	132		52	Protocol Amendment: Change in Protocol	Amendment 2: Based on the 11 Sept 07 Communication from the Division the protocol was revised to exclude subjects with PORT Risk Score II. This change in the protocol may be reversed pending the outcome of the Anti-infective Drugs Advisory Committee meeting planned for 1st quarter 2008.	P903-09
15-Oct-07	131			IND Safety Report: Follow-up to Written Report	CRXA2007000054 Subject No. 2010-09032/ AVR Follow- up #2:	P903-09
15-Oct-07	130			IND Safety Report: Follow-up to Written Report	CRXA2007000053 Subject No. 2012-06611/ MAB Follow- up #1: Additional information provided regarding treatment and event resolution.	P903-06
08-Oct-07	129		51	Other: Request for Division Comment Statistical Analysis Plan: P903-06/ -07	Statistical Analysis Plan (SAP) Tables, Figures, Listing Shells	P903-06 P903-07

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
05-Oct-07	128		51	IND Safety Report: Follow-up to Written Report	CRXA2007000054 Subject No. 2010-09032/ AVR Follow- up #1: Additional information regarding corrective treatment, relevant tests, hospital discharge date and study start and stop date added.	P903-09
05-Oct-07	127		51	Protocol Amendment: New Protocol	P903-18 Protocol including New Investigator 1572 and CV & Medical Monitor CV: Doug Rank, MD, TOO safety to Covance	P903-18
05-Oct-07	126		51	IND Safety Report: Follow-up to Written Report	CRXA2007000048 Subject No. 5014-07467/ NAR, Acute renal failure [Renal failure acute], Follow- up #2:	P903-07
05-Oct-07	125		51	Other: Closed IND Safety Report	CRXA2007000003 Event: Hypertension, Pre Renal azotemia Investigator Causality: Possibly related Case Outcome: Recovered Date of Initial Receipt/ Case Closure: 12 March 2007/ 18 Sept. 2007 Related Submissions: 04Apr07 #0072 & 24Apr07 #0079	P903-07
05-Oct-07	124		50	IND Safety Report: Follow-up to Written Report	CRXA2007000043 Subject No. 6515-07368/ IBA Follow- up #2: Additional information regarding addition of hospital discharge date, blood pressure and heart rate results and clindamycin stop date and amended event description and treatment details.	P903-07
28-Sep-07	123		50	Protocol Amendment: New Investigator	P903-06 and P903-07 New Investigator 1572 and CV	P903-06 P903-07
27-Sep-07	122		50	Protocol Amendment: New Investigator	P903-09 New Investigator 1572 and CV	P903-09
27-Sep-07	121		50	IND Safety Report: Initial Written Report	CRXA2007000053 Subject No. 2012-06611/ MAB Event: Hypersensitivity Reaction [Hypersensitivity]	P903-07

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27-Sep-07	120		50	IND Safety Report: Follow-up to Written Report	CRXA2007000048 Subject No. 5014-07467/ NAR Follow- up #1:	P903-07
26-Sep-07	119		50	IND Safety Report: Initial Written Report	CRXA2007000054 Subject No. 2010-09032/ AVR Event: Pleural Effusion [Pleural effusion]	P903-09
25-Sep-07	118		50	Other: Revised Form FDA-1572	P903-04 Principal Investigator's with Revised Form 1572	P903-04
25-Sep-07	117		50	IND Safety Report: Follow-up to Written Report	CRXA2007000004 Subject No. 0003-07006/ S-S Follow- up #3: Additional information provided regarding addition of analysis of similar events and correction of date of event in Box B3.	P903-07
25-Sep-07	116		50	IND Safety Report: Follow-up to Written Report	CRXA2007000028 Subject No. 0026-07208/ WLM Follow- up #2: Additional information regarding the event term, study drug start date, last date of study drug and analysis of similar events.	P903-07
25-Sep-07	115		50	IND Safety Report: Follow-up to Written Report	CRXA2007000044 Subject No. 5105-0922 Follow- up #1: Drug event relationship changed to unrelated, treatment medications added, start date of study drug added, X-ray result added, outcome of the event added.	P903-07
25-Sep-07	114		50	IND Safety Report: Initial Written Report	CRXA2007000048 Subject No. 5014-07467/ NAR Event: Acute renal failure [Renal failure acute]	P903-07
19-Sep-07	113		50	IND Safety Report: Follow-up to Written Report	CRXA2007000043 Subject No. 6515-07368/ IBA Follow- up #1: Additional information regarding primary site, culture results, patient's age, medical history, primary site infection treatment details, date of laboratory tests, definition of centralization, concomitant medication added	P903-07

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
19-Sep-07	112		50	IND Safety Report: Follow-up to Written Report	CRXA2007000040 Subject No. 6511-07312/ D-K Follow- up #3: Treatment details amended, discharge date amended, details of 2nd chemotherapy added	P903-07
13-Sep-07	111		50	IND Safety Report: Initial Written Report	CRXA2007000044 Subject No. 5105-09022 Event: Pulmonary abscess (lung abscess)	P903-09
14-Sep-07	110		50	IND Safety Report: Follow-up to Written Report	CRXA2007000040 Subject No. 6511-07312/ D-K Follow- up #2: Additional information regarding amending event details, addition of CLL description, clarification of aetiology, addition of blood culture results, addition of dates to concomitant medication administration, updated analysis of similar medical events and gender correction.	P903-07
11-Sep-07	109		50	IND Safety Report: Initial Written Report	CRXA2007000043 Subject No. 6515-07368/ IBA Event: Anaphylactic Shock [Anaphylactic Shock]	P903-07
31-Aug-07	108		50	IND Safety Report: Follow-up to Written Report	CRXA2007000040 Subject No. 6511-07312/ D-K Follow- up #1: Additional information provided regarding medical history, concomitant medication, study drug start date, treatment, test results, and date of hospitalization.	
31-Aug-07	107		50	IND Safety Report: Follow-up to Written Report	CRXA2007000039 Subject No. 2006-06444/ AJB Follow- up #1: Additional information provided regarding study drug dates, blood cultures, concomitant medication, treatment and primary site of infection.	P903-06

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24-Aug-07	106		50	IND Safety Report: Initial Written Report	CRXA2007000040 Subject No. 6511-07312/D-K Event: Clinical worsening [Condition aggravated]	P903-07
24-Aug-07	105		50	Protocol Amendment: New Investigators	P903-09 New Investigator 1572 and CV	P903-09
23-Aug-07	104		50	IND Safety Report: Initial Written Report	CRXA2007000039 Subject No. 2006-06444/ AJB Event: Hypersensitivity Reaction	P903-06
23-Aug-07	103		50	Other: Revised Form FDA-1572	P903-06 & P903-07 Principal Investigator's with Revised Form 1572	P903-06 P903-07
23-Aug-07	102		50	Protocol Amendment: New Investigators	P903-06 and P903-07 New Investigator 1572 and CV	P903-06 P903-07
14-Aug-07	101		50	IND Safety Report: Follow-up to Written Report	CRXA2007000028 Subject No. 0026-07208/ WLM Follow- up #1: Additional information provided regarding event resolution, resolution date of 01 AUG 07, and additional laboratory results	P903-07
14-Aug-07	100		50	OTHER: Request for Division Comment: Pediatric Development Plan	Request for Division comments on proposed pediatric plan Ceftaroline for Injection Synopsis for Protocol P903-15	P903-15
27-Jul-07	99		50	IND Safety Report: Initial Written Report	CRXA2007000028 Subject No. 0026-07208/ WLM Event: Worsen prolonged clotting times	P903-07
16-Jul-07	98		50	Protocol Amendment: New Investigator	P903-09 New Investigator 1572 and CV	P903-09
19-Jul-07	97		50	Protocol Amendment: New Investigators	P903-06 and P903-07 New Investigator 1572 and CV	P903-06 P903-07
16-Jul-07	96		50	Protocol Amendment: Change in Protocol	P903-09 CAP Protocol Amendment 1	P903-09
09-Jul-07	95		50	Information Amendment: Chemistry/ Microbiology	Revised specifications for related substances U-5, U-7 to U-9	

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
19-Jun-07	94		49	Response to Division Comments dated 07 June 2007	Cerexa's response to Divisions question on P903-08 and P903-09 CAP (reference to Division's comments dated 15 March 2007 received by email)	P903-08 P903-09
18-Jun-07	93		49	Protocol Amendment: Change in Protocol	P903-17 IM Protocol Amendment 1 (change: change in PK sampling), Medical Monitor CV: Ed Fong	P903-17
15-Jun-07	92		49	Protocol Amendment: New Protocol	P903-09 CAP Protocol including New Investigator 1572 and CV, Transfer of Obligation (TOO) information, Medical Monitor CV: Paul Eckburg	P903-09
18-Jun-07	91		49	Protocol Amendment: New Investigators	P903-06 and P903-07 New Investigator 1572 and CV	P903-06 P903-07
14-Jun-07	90		49	Information Amendment: Pharmacology/ Toxicology	nonclinical study report: P0903-T-015	
14-Jun-07	89		49	Information Amendment: Clinical	Investigator's Brochure and corresponding summary of changes Edition 8, dated 23 May 2007, supersedes edition 7, dated 20 September 2006	
14-Jun-07	88		49	Protocol Amendment: New Protocol	P903-17 IM Protocol including New Investigator 1572 and CV	P903-17
01-Jun-07	87		49	Response to FDA Request for Information	Submission of "highlights of clinical pharmacology" for P903-05 Thorough ECG trial (TET) protocol requested by FDA on 21 May 2007 via email. Reference is made to submission 082 protocol submission and request for comments.	P903-05
29-May-07	86		49	Response to FDA Request for Information	Mini briefing book for Type A meeting scheduled for 07 June 2007. Related submission 075 and 076 "Request for Meeting" for non-inferiority justification	

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
18-May-07	85		49	Protocol Amendment: New Investigators	New investigator 1572 and CV for P903-06 and P903-07	P903-06 P903-07
10-May-07	84		49	Information Amendment: Chemistry/ Microbiology	Nonclinical study report: P0903-M-018	
10-May-07	83		48	Information Amendment: Pharmacology/ Toxicology	nonclinical study reports: P903-T-014, P0903-P-006, P0903-P-007, P0903-P-008	
08-May-07	82		48	Information Amendment: Clinical	P903-05 Thorough ECG trial (TET) protocol requesting FDA review/comments	P903-05
04-May-07	81		48	IND Safety Reports: Follow-up to Written Report	CRXA2007000004 Anaphylactoid reaction/anaphylactic reaction, Subject No. 0003-07006 Follow-up 2	P903-07
09-May-07	80		48	Protocol Amendment: Change in Protocol	P903-06 and P903-07 Protocol Amendment 2 (change: increase sample size, modification of Vancomycin dose, addition of PK)	P903-06 P903-07
24-Apr-07	79		48	IND Safety Reports: Follow-ups to Written Reports	Follow-up safety reports for CRXA2007000003-Subject No. 0028-07002 CRXA2007000004-Subject No. 0003-07006	
20-Apr-07	78		48	Protocol Amendment: New Investigators	Fourth investigator submission for cSSSI. Twenty three (23) investigators were submitted	P903-06 and P903-07

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
17-Apr-07	77		47	Other: Response to Division Comments	Dated 15 March 2007 Related to the Special Protocol Assessment: Community - acquired Pneumonia	
12-Apr-07	76			Other: Request for Type A Meeting	Request meeting to discuss changes to protocol P903-08 Mini briefing document for discussion	P903-08
12-Apr-07	75		47	Other: Request for Type A Meeting	Request meeting to discuss the NI margin for protocol P903-08 and P90-09	P903-08 P903-09
06-Apr-07	74		47	Response to FDA Request for Information	Response to microbiology comments – Laboratory Manuals included	
06-Apr-07	73		47	IND Safety Report: Initial Written Report	CRXA2007000004 Sub: 0003-07006/S-S Anaphalactoid Reaction [Anaphylactic reaction]	P903-07
04-Apr-07	72			IND Safety Report: Initial Written Report	CRXA2007000003 Sub: 0028-07002/TJB Hypotension [hypotension], Pre-renal azoternia [acute prerenal failure]	P903-07
04-Apr-07	71			Protocol Amendment: New Protocol	Original Protocol P903-04 (renal study), investigator 1572 and CV	P903-04
05-Apr-07	70			Other: Response to Division Comments Dated 07 February 2007	Ceftaroline fosamil Other: Response to Division Comments Dated 07 February 2007	
21-Mar-07	69		45	Other: New Form FDA 1571	USAN name change to ceftaroline fosamil	
21-Mar-07	68		45	Protocol Amendment: New Investigators	New Investigator 1572 and CV	P903-06 P903-07
15-Mar-07	67		38 through 44	Information Amendment: Pharmacology-Toxicology	Submission of preclinical reports: Microbiology,: P0903-M-004/011, P0903-M-016, P0903-M-020 Toxicology: P0903-T-010, P0903-T-011, P0903-T-012, P0903-T-013 (9 volumes)	
13-Mar-07	66		37	Annual Report	Second Annual Report (Report period: 13Jan2006-12Jan2007)	
09-Mar-07	65		37	Response to FDA Request for Information	Literature referenced in ser. 062, in response to request of 09-Mar-07	

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
21-Feb-07	64		37	Protocol Amendment: New Investigators	New Investigator 1572 and CV	P903-06 P903-07
26-Jan-07	63		37	Other: Request for Special Protocol Assessment	Special Protocol Assessment (Protocol P903-09)	P903-09
26-Jan-07	62		37	Other: Request for Special Protocol Assessment	Special Protocol Assessment (Protocol P903-08)	P903-08
18-Jan-07	61		36	Response to FDA Request for Information	Submission of references in support of justification of the 10% non-inferiority margin	
16-Jan-07	60		36	Protocol Amendment: Change in Protocol	Submission of Amendment 1 for protocols P903-06, and P903-07.	P903-06, Am1 P903-07, Am1
16-Jan-07	59		36	Protocol Amendment: New investigator	New Investigator 1572 and CV	P903-06 P903-07
16-Jan-07	58		36	Information Amendment: Chemistry/Microbiology	Proposal for Provisional Interpretive Criteria for Ceftaroline	
16-Jan-07	57		36	Other: Response to Comments Dated 15 November 2006	Attachment 1: Response to comments Attachment 2: Microbiology Laboratory Manual	
01-Dec-06	56		36	Information Amendment: Chemistry-Microbiology/ Pharmacology-Toxicology	Blend data in CTD format	
22-Nov-06	55		36	Other: Response to Division Comments	Response to division comments dated 20 October 2006, NI justification for cSSSI	
10-Nov-06	54		36	Protocol Amendment: New Protocol	Original Protocols P903-06 and P903-07, TOO information	P903-06 P903-07
27-Oct-06	53		35	Other: Minutes from EOP2 teleconference held 24 October 2006	Cerexa's Minutes from EOP2 teleconference held 24 October 2006	
24-Oct-06	52		35	Other: Agenda for EOP2 Teleconference of 24 October 2006	Meeting Agenda for End of Phase 2 Teleconference - 24 October 2006	

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
17-Oct-06	51		35	Information Amendment: Chemistry-Microbiology/ Pharmacology-Toxicology	Submission of nonclinical report number P0903-M-010	
21-Sep-06	50		35	Other: Briefing book for EOP2 meeting	Briefing book for EOP2 meeting	
08-Sep-06	49		34	Information Amendment: Chemistry-Microbiology/ Pharmacology-Toxicology	Submission of nonclinical report numbers P0903-M-006, P0903-M-012, and P0903-P-004	
21-Aug-06	48		34	Other: Reschedule EOP2 Meeting	Request for rescheduling the EOP2 meeting during the week of 16 October.	
17-Aug-06	47		34	Information Amendment: Chemistry-Microbiology/ Pharmacology-Toxicology	Submitting final Pre-Clinical Reports (P0903-M-007/P0903-M-008; P0903-M-014; P0903-P-005). P0903-M-007/M-008 was resubmitted because pages were missing in the original submission in Serial #41 due to photocopying error.	
04-Aug-06	46		33	Other: Revised Form FDA-1572	Submitting revised 1572 w/correct name for Focus and addition of a ethics committee.	P903-03
04-Aug-06	45		33	Other: Revised Form FDA-1571	Submitting Updated Chemical Name from USAN Adoption Letter that was used in the CMC End of Phase 2 Meeting in Serial. 43	
31-Jul-06	44		33	Other: Request for Type B Meeting)	Request for Type B Meeting (End of Phase 2)	EOP2
31-Jul-06	43		33	Other: Request for Type C Meeting: CMC	Request for Type C Meeting (End of Phase 2 CMC)	EOP2: CMC
23-May-06	42		33	Other: Revised Form FDA-1572	Adding New Subinvestigators to P903-03 site (Vivar Mendoza)	P903-03

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
23-May-06	41		33	Information Amendment: Chemistry-Microbiology/ Pharmacology-Toxicology	Submitting final Pre-Clinical Reports (P0903-T-03; P0903-T-42; P0903-M-005; P0903-M-007/P0903-M-008; P0903-M-013); In vitro genetic toxicity testing on active metabolite (FDA request in FDA 05Aug05 ltr); P0903-M-005 response to FDA request to assess why c	
23-May-06	40		33	Other: Revised Form FDA-1571	Submitting Updated Chemical Name from USAN Adoption Letter	
27-Apr-06	39		33	Other: Revised Form FDA-1571	Submitting USAN name ceftaroline acetate	
28-Mar-06	38		33	Information Amendment: Pharmacology-Toxicology	Submitting final Pre-Clinical Reports (P0903-P-001; P0903-P-002; P0903-P-003)	
23-Mar-06	37		33	Protocol Amendment: New Investigator	Submitting new investigator for P903-03	P903-03
23-Mar-06	36		33	Information Amendment: Chemistry/ Microbiology	Submitting Infusion Solution Stability Study Results; Support for use period in clinical study of 24 hours refrigerated followed by 6 hours of room temperature	
07-Mar-06	35		33	Annual Report	First Annual Report (Report period: 13Jan2005-12Jan2006)	
22-Feb-06	34		33	Information Amendment: Chemistry/ Microbiology	New manufacturer information for DMF Type III, N 17506 Sterbag Packaging System (Facta to ACS Dobfar)	
22-Feb-06	33		33	Other: Revised Form FDA-1572	Adding New Subinvestigators to P903-02 sites (Swan and Marbury); Correcting Focus Bio-Inova, Inc name on Rodriquez (P903-03) 1572	P903-02, P903-03
22-Feb-06	32		33	Protocol Amendment: New Investigator	Submitting new investigator for P903-03	P903-03
22-Feb-06	31		33	Other: Revised Form FDA-1571	Submitting other research identifier (PPI-0903 Injection, TAK-599); Change title of Mary O'Hara Zimmerman to VP	

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
13-Jan-06	30		33	Information Amendment: Chemistry/ Microbiology	Submitting drug labels for P903-02, P903-03	P903-02, P903-03
12-Jan-06	29		33	Protocol Amendment: New Investigator	Submitting new investigator for P903-03	P903-03
30-Dec-05	28		32	Other: Request for Fast Track Destination	Submitted Request for Fast Track Destination	
21-Dec-05	27		32	Protocol Amendment: Change in Protocol	Submitted P903-03 Amendment 2 and Summary of Protocol Changes; inclusion of mild renal subjects	P903-03
16-Dec-05	26		32	Other: Revised Form FDA-1572	Submitting Revised 1572 w/ new sub-investigator information	P903-03
11-Nov-05	25		32	Other: Revised Form FDA-1572	Submitting Revised 1572 w/ new sub-investigator information	P903-02
11-Nov-05	24		32	Protocol Amendment: New Investigator	Submitting new investigator for P903-03	P903-03
12-Oct-05	23		32	Protocol Amendment: New Investigator	Submitting new investigator for P903-03	P903-03
27-Sep-05	22		32	Protocol Amendment: Change in Protocol	Submitted P903-02 Amendment 5 and Summary of Protocol Changes	P903-02
12-Sep-05	21		32	Response to FDA request for information	Response to FDA official comments dated 05Aug2005	P903-03; IND
12-Sep-05	20		32	Protocol Amendment: New Investigator	Submitting new investigator for P903-03	P903-03
12-Sep-05	19		32	Protocol Amendment: New Protocol	Submitting P903-03 Amendment 1; Original draft was submitted as #009; Transfer of responsibility statement included in cover letter	P903-03
08-Sep-05	18		32	Other: Revised Form FDA-1572	Submitting Revised 1572 w/ new sub-investigator information	P903-02
11-Jul-05	17		32	Protocol amendment: Change in Protocol	Submitted P903-02 Amendment #4 and Summary of Protocol Changes	P903-02
11-Jul-05	16		32	Information Amendment: Clinical	Submitted IB Edition 6; Changing PPI to Cerexa.	

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
07-Jul-05	15		32	Other: Revised Form FDA-1571	Submitting Revised 1571 w/ new Sponsor, Medical Monitor, Contact person. Medical Monitor CV enclosed	
30-Jun-05	14		31	Other: Transfer of IND Sponsorship	Change of Sponsorship to Cerexa and contact person to MOZ.	
03-May-05	13		31	Response to FDA request for information	Response to FDA official comments dated 08Apr2005	Original IND
25-Apr-05	12		31	Information Amendment: Clinical	Submitting final Bioanalytical report referenced in PK report previously submitted w/ original IND and Ser. 003	
25-Mar-05	11		31	Information Amendment: Clinical	Submitting updated IB (edition 5, dated March 18, 2005)	
10-Mar-05	10		31	IND Safety Report: Follow Up	Submitting final toxicology report. Previously submitted in Ser. 005 (IND Safety Report).	
09-Mar-05	9		31	Protocol Amendment: New Protocol	Submitting P903-03	P903-03
09-Mar-05	8		30	Information Amendment: Pharmacology-Toxicology	Submitting two final toxicology report. Previous submitted in IND and serial no. 5 (Safety Report).	
28-Feb-05	7		29	Protocol amendment: Change in Protocol	Submitting Amendment 2 of P903-02	P903-02
12-Feb-05	6		29	General Correspondence	Letter to FDA: Requesting acknowledgement of receipt of IND.	
08-Feb-05	5		29	IND Safety Report: Initial	Submitting preliminary safety data from toxicology study in rabbits.	
08-Feb-05	4		29	Protocol amendment: new investigator	Submitting new investigator for P903-02	P903-02
02-Feb-05	3		28	Information Amendment: Clinical	Submitting Final PK report for P903-01	P903-01
01-Feb-05	2		28	Protocol amendment: Change in Protocol	Submitting Amendment 1of P903-02	P903-02
19-Jan-05	1		28	General correspondence	Change in PPI regulatory contact to Sharon Powell	

Date	Serial No.	FDA Serial No.	Book No.	Submisssion/Correspondence Type	Content	Protocol
10-Dec-04	0		Book 1-27	Original IND submission	Original IND for PPI-0903 (Volumes 1-27).	P903-02

NDA CORRESPONDENCE LOG

Date of Correspondence	Book No.	Communication Type	Description	Protocol
24-Dec-09		General	Informing FDA of timing of upcoming NDA submission	
30-Dec-09		General	Notifying FDA and providing the Automatic Receipt that the NDA has been received through the gateway	
30-Dec-09 a		General	ROC: contacting FDA to get verbal confirmation that they have received the NDA in the electronic document room	
04-Jan-10		General	Acknowledgement from FDA that the NDA has arrived	
11-Jan-10		FDA Letter	FDA letter acknowledging receipt of NDA. 60-day review period ends 2/28/10	
12-Jan-10		Response/comments	Division of Scientific Investigations (DSI) requested summary level clinical site data for data integrity review and inspection planning	
13-Jan-10		Response/comments	Call from FDA requesting location of Establishment Information in the NDA	
13-Jan-10 a		Response/comments	FDA request the location of the pediatric assessment in the NDA	
14-Jan-10		Response/comments	FDA request we resubmit the PPSR to satisfy the pediatric assessment	
14-Jan-10 a		General	Wendy Gill email to esubs on the proper way to submit the revised datasets	
14-Jan-10 b		Response/comments	Providing summary of dataset changes for Phase 3 studies and requesting a telecon	
15-Jan-10		General	Request meeting to talk about dataset changes	
19-Jan-10		General	Response from CDER eData to Wendy Gill on the proper way to submit the revised datasets	Phase 3
20-Jan-10		General	Cerexa cancels meeting to discuss Phase 3 datasets since received notification from CDER eData group	Phase 3
21-Jan-10		General	Carmen Debellas(FDA) emailed asking when they could expect the datasets. SG responded that they would be there on 1/25	
29-Jan-10		General	FDA Reviewer unable to view CMC Module	
01-Feb-10		Response/comments	Wendy Gill email to esubs regarding CMC dataset review issue. Preston Whitaker GlobalSubmit Product Support response attached.	

02-Feb-10		Response/comments	FDA Reviewer unable to view CMC Module. Cerexa suggest converting to excel. Excel should be filed to NDA.	
02-Feb-10 a		Response/comments	Agency provides guidance on how to satisfy pediatric assessment (request from PM 13Jan10)	
23-Feb-10		Response/comments	Question from IRT/QT review team 17-Feb-10 Carmen request for slopes of QTclb and QTclc, 19-Feb-10 Carmen clarifies request, 23-Feb-10 Cerexa response to location of QT dataset in the NDA	P903-05
24-Feb-10		Response/comments	Response to IRT/QT review team dated 23-Feb-10 was sufficient.	P903-05
25-Feb-10		General	Confirming no outstanding items before the 60 day review period. Confirm the issue letter will contain priority review status.	
01-Mar-10		General	Cerexa request call in with Carmen to discuss NDA's fileability at day 60.	
02-Mar-10		General	Telecon with FDA to discuss the NDA's fileability at day 60, priority review status, 120 day safety report, AC meeting, and Carmen's contact during his medical leave.	
04-Mar-10		General	Emailed Francis LeSane to ensure Cerexa had the right email address.	
17-Mar-10		General	Called and emailed interim PM Frances LeSane regarding the fileability letter and NDA questions.	
19-Mar-10		General	Emailed interim PM Frances LeSane and Jeannie Davis regarding the fileability letter and NDA questions.	
25-Mar-10		Response/comments	electronic version - Response to starting material submitted for comments to FDA Oct. 2, 2009	
03/25/2010 a		Response/comments	official comments for CMC - starting material and NDA comments (received via mail Apr. 1, 2010)	
26-Mar-10		FDA Letter	Official copy of filability letter (does not contain questions on dataset) (received via mail 06Apr10)	
30-Mar-10		General	Request for information: Status of fileability letter and questions, how to request a informational meeting, topics of the April 29 AC meeting, status of Carmen DeBellas	
01-Apr-10		General	Request copy of fileability letter and NDA comments via email	

2-Apr-10		Response/comments	Cerexa request a meeting to discuss how we should submitt the PK error summary.	
02-Apr-10 a		Response/comments	email copy of filability letter and request for datasets	
07-Apr-10		Response/comments	DSI request list of Phase 3 CRO monitors	
07-Apr-10 a		FDA Letter	Proprietary Name Request unacceptable. Resubmit APTARIN (received via mail 13Apr10)	
08-Apr-10		Response/comments	Email of DSI request for Phase 3 CRO	
09-Apr-10		General	Forward email to DSI (8Apr10) to Carmen DeBellas	
12-Apr-10		Response/comments	Pharmacology comments re. thawed samples from study P903-01	SN 0000, P903-01
14-Apr-10		Response/comments	email Carmen and Jeannie NDA SN 0008, response to starting material submission and CMC question in fileability letter	SN 0008
19-Apr-10		Response/comments	Dataset request - phase 3 CABP, request for con meds considered antipyretic	P903-08, P903-09
19-Apr-10 a		General	Request date for AC meeting	
19-Apr-10 b		General	Telecon agenda for 4/20 call	
20-Apr-10		Response/comments	Pharmacology comments re. P903-13. Provide validation data to ensure CPT urine concentration did not exceed the upper limit of standard curve range	P903-13
20-Apr-10 a		General	ROC: discussed proprietary name, AC meeting, pediatric plan and deferral, sponsor audit, NDA communication, PM retirement plans	
21-Apr-10		General	Provide PM DSI minutes: request for list of CRO (4/7/10) and inquiry of location of files (4/14/10)	
21-Apr-10 a		General	AC meeting logistics - BB, presentation, safety, Q&A	
22-Apr-10		General	AC meeting logistics - safety, location	
23-Apr-10		Response/comments	CMC comments (received 30Apr10 via mail)	
28-Apr-10		General	AC meeting logistics - FDA response to safety presentation and location	
30-Apr-10		General	AC meeting logistics - FDA response to safety presentation	
30-Apr-10 a		General	Inform FDA that Cerexa received the CMC comments. Request that an electronic copy of comments be provided to avoid delay in the response.	
03-May-10		General	Asked Advisor and Consultant group (Minh Doan) location of the AC meeting in Sept.	

10-May-10		Audit/inspections	Dr. Marisa M. White request information on Russian sites for audit	
11-May-10		Audit/inspections	Richard Reeve left message with Dr. Marisa White	
12-May-10		Audit/inspections	site inspection anouncement: Georgia	
12-May-10 a		Audit/inspections	site inspection anouncement: Ukraine	
13-May-10		Audit/inspections	inspection fu: Ukraine	
13-May-10 a		Audit/inspections	inspection fu: Georgia	
14-May-10		Audit/inspections	inspection fu: Russia. Letter stating inspection ready for sites: Popova, Konychev, Goryunov	
20-May-10		Audit/inspections	inspection fu: Russia. Business Visa	
20-May-10 a		Response/comments	Request for all new datasets with consistant patient id numbering (request made 18May10 via email)	
21-May-10		Audit/inspections	inspection fu: Ukraine. Letter stating inspection ready for sites: Kraydashenko and Yashyna	
21-May-10 a		Audit/inspections	inspection fu: Georgia. Status on Tabukashvili	
24-May-10		Audit/inspections	inspection fu: Russia hotels	
26-May-10		Response/comments	FDA requested a meeting to present how they plan to analyze the data in the NDA (meeting June 1, 2010) Discuss submission timing of datasets (FDA request 18May10) Discussed proprietary name Discussed audits in Ex-US	
27-May-10		Response/comments	FDA request CRFs for subjects with missing data on Day 4 (received via email 27May10)	
28-May-10		FDA Letter	AC meeting July 7, 2010 logistics	
28-May-10 a		Audit/inspections	inspection fu Russia: Mr Fleckenstein's itinerary and hotel	
04-Jun-10		General	Cerexa and FDA attendee list from June 1, 2010 telecon with FDA	
04-Jun-10 a		Response/comments	Comments on analysis population and efficacy endpoint for cSSSI and CABP. Document discussed on June 1, 2010 meeting	
07-Jun-10		General	Carmen checking if we received comments on analysis population and effecacy endpoint	
08-Jun-10		Response/comments	Clinical Pharmacology Reviewer request: provide files for population PK reports 174-3 and 174-4	
09-Jun-10		Response/comments	Emailed Minh Doan on where Cerexa should submit the requested items from the AC letter.	

01-Jun-10		Meerting Minutes	internal meeting minutes: meeting regarding additional sensitivity analysis planned by the FDA	
10-Jun-10		Response/comments	Response to AC letter: List of Investigators and preliminary Meeting Participants	
10-Jun-10 a		General	AC meeting logistics: copies to be sent to PM Carmen DeBellas and NDA	
10-Jun-10 b		Audit/inspections	Ukraine inspection: request for protocol	
16-Jun-10		Response/comments	AC logistics: propose AC meeting agenda. FDA response on presentation timing.	
23-Jun-10		General	Notifying Jeannie David of CMC submission SN 0020 (stability report for 12 month data)	
24-Jun-10		Response/comments	Clinical Information request: Request for additional information from subjects in P903-06, P903-07 and P903-08. FDA clarified information needed to assess association of drug to deaths/SAEs leading to death.	
24-Jun-10 a		Response/comments	Response to 4Jun10 document from FDA on CABP additional analysis	
28-Jun-10		Response/comments	Request for P903-06 and P903-07 CRF	
30-Jun-10		Response/comments	FDA revised request to 4Jun10 document on CABP additional analysis. Cerexa's request for clarification.	
02-Jul-10		Response/comments	FDA response to Cerexa's request for clarification dated 29Jun10 (see corr. Dated 30Jun10). Additional request for P903-08 and P903-09 CRFs	
06-Jul-10		General	Location of AC meeting (also available in FR Notice website)	
07-Jul-10		Response/comments	Request status of 4Jun10 document. Status of cSSSI response	
08-Jul-10		Response/comments	Question about the pediatric plan and NDA, are the documents linked.	
13-Jul-10		General	contact information on Industry Representative at the Cerexa AC meeting. Dr. Joe Camardo	
14-Jul-10		General	1. Status on the comments on analysis population and efficacy endpoint for cSSSI (clarification on the June 4 document from FDA) 2. Status on the request to include H. Parainfluenzae as a pathogen in CABP 3. Response to Cerexa email (July 8, 2010) on the pediatric plan, deferral, and PPSR relative to NDA approval	

14-Jul-10 a		General	Follow-up to discussion on 14-Jul-10. Provide cSSSI comments that need a response from the Clinical Reviewer	
15-Jul-10		General	Forward information about the Cerexa site audit	
20-Jul-10		Response/comments	Microbiology question regarding Streptococcus pneumoniae	
20-Jul-10 a		Response/comments	Response to cSSSI and CABP additional endpoints provided June 4 (clarification request provided NDA SN 0019). Additional request for information	
21-Jul-10		Response/comments	Another Microbiology question regarding H. parainfluenzae and H. influenzae	
26-Jul-10		Response/comments	Copy of response to microbiology questions (from 20Jul and 21Jul).	
28-Jul-10		Response/comments	CMC questions - PI change and USAN clarification	
29-Jul-10		General	AC logistics - shipment of BB	
29Jul10 a		General	AC logistics - BB addendum, separate BB for each indication, CD of BB	
02-Aug-10		Response/comments	Cerexa vs. FDA - differences in CABP additional analysis (missmatch)	
03-Aug-10		Response/comments	Response to CMC comment provide 28Jul10	
04-Aug-10		General	Minh confirmed she received the breifing books for the AC meeting	
04-Aug-10 a		General	Contacted Carmen and Jeannie about getting a audit waiver for ACS Dobfar	
04-Aug-10 b		Response/comments	Clinical Pharmacology Reviewer request: clarification to ICPD 00174-8 and ICPD 00174-9 AUC value	
05-Aug-10		General	Confirming Carmen received his copies of the briefing book.	
05-Aug-10 a		Response/comments	Clinical Pharmacolgoy Review request: provide datasets for ICPD 00174-8 and ICPD 00174-9	
05-Aug-10 b		General	-Requested timing on getting the cSSSI Reviewers comments on the mix-match between Cerexa and FDA additional analysis. -Carmen confirmed reciept of 10 copies of briefing book.	
06-Aug-10		Response/comments	Provide Carmen copy of Cerexa's response to missmatch identified by FDA on the CABP additional analysis (comments 02Aug10)	
12-Aug-10		General	ROC: Request clarification on the final list of attendees for the AC meeting	

13-Aug-10		Response/comments	-Status of the FDA BB -FDA response to Cerexa's comment on the mismatch CABP additional analysis (FDA response to NDA SN 0030)	
13-Aug-10 a		Response/comments	Cerexa vs. FDA - differences in cSSSI additional analysis (mismatch)	
13-Aug-10 b		General	Informing Cerexa that the FDA BB will be sent on CD	
16-Aug-10		Response/comments	More Cerexa vs. FDA - differences in cSSSI additional analysis (mismatch)	
17-Aug-10		FDA Letter	FDA Briefing Book	
18-Aug-10		General	Final list of Speakers and Responders	
19-Aug-10		Response/comments	Request clarification on cSSSI secondary endpoints (received on 16Aug10)	
19-Aug-10 a		Response/comments	Heads up - requesting meeting to discuss break point information in the FDA BB	
19-Aug-10 b		General	Request clarification on how to provide errata/corrections to the FDA BB	
19-Aug-10 c		Response/comments	FDA response to Cerexa's clarification question provided 19Aug10 regarding cSSSI secondary endpoint request from FDA (16Aug10)	
19-Aug-10 d		Response/comments	Cerexa response to the FDA AIDAC briefing book - request for meeting to discuss proposed in vitro susceptibility test interpretation criteria (breakpoint)	
20-Aug-10		Response/comments	Cerexa submits the request for redaction to the FDA briefing book. FDA responds that they do not plan on redacting the briefing book. The breakpoint will be discussed during the AC meeting.	
23-Aug-10		General	Updated list of AIDAC presenters and responders. FDA requesting Dr. Ambrose to follow MAPP	
24-Aug-10		General	Meeting logistics for 26Aug10 meeting to discuss FDA briefing book	
24-Aug-10 a		General	Provide Cerexa briefing book addendum to FDA PM and AIDAC PM	
25-Aug-10		Response/comments	Information request - additional analysis for studies P903-06/-07	
26-Aug-10		General	Cerexa briefing book addendum with correct cover page and footer to FDA PM and AIDAC PM	
26-Aug-10 a		Meeting Minutes	Meeting minutes from 26 Aug 10 informal telecon to discuss breakpoint differences in AC briefing books	
27-Aug-10		General	Request AC member list and questions	
30-Aug-10		General	Attendee list from August 26th meeting	

30-Aug-10 a		Response/comments	FDA listing of patients as a follow-up to the 26 Aug 2010 telecon	
30-Aug-10 b		Meeting Minutes	Meeting minutes from 30Aug10 telecon on clarification to FDA information requeset dated 25Aug10	
31-Aug-10		Response/comments	Provide FDA list of clarification questions from 25Aug10 Request for Additional Informaiton for P903-06/-07. Includes attendee list.	
31-Aug-10 a		FDA Letter	FDA letter on final logistics for the 07Sep10 AIDAC meeting	
31-Aug-10 b		Response/comments	Submission of Cerexa action item from 25Aug10 information request and 30Aug10 telecon	
01-Sep-10		General	Dr. Ambrose received Director approval to participate in AIDAC as a sponsor representative	
02-Sep-10		Response/comments	Errata to FDA briefing book was provided and email stating FDA not issuing errata	
02-Sep-10 a		General	AC logistics - monitors	
02-Sep-10 b		General	Attendee list clarification	
02-Sep-10 c		Response/comments	Cerexa tables as an action item from 25Aug10 information request and 30Aug10	
03-Sep-10		Response/comments	Data from Dr. Bhattacharya site and all India sites form P903-09 will be excluded from the FDA analysis at the AC meeting	
13-Sep-10		General	Request whe PeRC meeting will occur and inform that the protocol will be submitted to IND.	
14-Sep-10		Response/comments	FDA requesting analysis that was requested on 25Aug10. Cerexa requested clarification on FDA's request	
14-Sep-10 a		General	Request status of label negotiations	
16-Sep-10		Response/comments	Informing FDA tables that will be provided to respond to 25Aug10 FDA information request	
20-Sep-10		Response/comment	Cerexa informed/request the following: 1) status of the proposed proprietary name approval. PM said it was approved but official letter of approval will be provided 12Oct 2) informed the FDA that we have a new updated label for submission	
20-Sep-10 a		Response/comment	Provide updated package insert with changes highlighted	
21-Sep-10		Response/comment	Respond to FDA question about Module 1 Sec. 1.3.4 Financial Disclosure information	

23-Sep-10		Response/comment	Provide FDA Pediatric timeline for PREA studies	
30-Sep-10		FDA Letter	Inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.	P903-06, P903-07, P903-08, P903-09
08-Oct-10		FDA Letter	Proprietary Name Request Conditionally Acceptable	
29-Oct-10		FDA Letter	Approval letter	

NDA SUBMISSION LOG

Date	Serial No.	Submission Type	Content
30-Dec-09	0000	New Drug Application	Original signature and shadow copy for Module 1. All other Modules located in J drive
08-Jan-10	0001	Request for Proprietary Name Review	Proprietary Name - Emercef and Aptarin
20-Jan-10	0002	Response to FDA Request for Additional Information	Establishment Information
26-Jan-10	0003	Response to FDA Request for Additional Information	Division of Scientific Investigational Request Data (DSI) dataset
01-Feb-10	0004	Amendment to a Pending Application	Phase 3 datasets (CSR, SDTM, ISS, ISE) replaced in orignal NDA
29-Jan-10	0005	Response to FDA Request for Additional Information	Resubmission of DSI datasets. Includes number of subjects screened per site.
04-Feb-10	0006	Amendment to a Pending Application	Pediatric plan and deferral request to address missing Pediatric Assessment
09-Apr-10	0007	Response to FDA Request for Additional Information	Request for CRO Information
13-Apr-10	NA		DMF #23167 Dobfar (submitted by Dobfar to DMF)
14-Apr-10	0008	Response to FDA Information Request	1.11.1 Quality Information Amendment
23-Apr-10	0009	Amendment to a Pending Application	Correction to an Error in the Population Pharmacokinetic Analyses
23-Apr-10	0010	Response to FDA Request for Additional Information	Dataset Request and Statistical Questions
28-Apr-10	0011	Amendment to a Pending Application	120-Day Safety Update
29-Apr-10	0012	Response to FDA Information Request	Study P903-13 Clinical Pharmacology Comment
30-Apr-10	0013	Response to FDA Information Request	Study P903-01 Clinical Pharmacology Comment
03-May-10	0014	Response to FDA Information Request	Antipyretic Dataset Request
14-May-10	0015	Response to FDA Information Request	CMC comments
07-Jun-10	0016	Response to FDA Information Request	CRF for subjects missing data at day 4
02-Jun-10	0017	Response to FDA Information Request	Dataset request: unique patient identifier for each patient, that can be used across all data sets
18-Jun-10	0018	Response to FDA Information Request	Clinical Pharmacology Request: PK report 00174 3 and 00174-4 new dataset
21-Jun-10	0019	Response to FDA Information Request	Statistical Analyses: Requests for further clarification to the FDA's correspondence dated 04 June 2010 - comments on analysis population and efficacy endpoint for cSSI and CABP.
23-Jun-10	0020	Response to FDA Information Request: CMC - Additional Stability Data	Stability report submission for twelve (12) months data for the 400 mg strength. Follow-up to 14 April 2010 (SN 0008)

Date	Serial No.	Submission Type	Content
02-Jul-10	0021	Response to FDA Information Request: Additional Case Report Forms	Clinical Information Request: Provide CRFs for subjects in Study P903-06 and P903-07.
09-Jul-10	0022	Response to FDA Information Request	Clinical Request for Additional Information Leading to Subject Death
13-Jul-10	0023	Response to FDA Information Request: Request for Additional Case Report Forms	Request for Additional Case Report Forms
14-Jul-10	0024	Requst for Proprietary Name Review: Primary Name: TEFLARO	Proprietary Name Analysis for TEFLARO for review by the Div. of Medication Error Prevention and Analysis (DMEPA), OSE.
20-Jul-10	0025	Response to FDA Information Request: Statistical Analyses	Includes all requested info for CABP inidcation.
26-Jul-10	0026	Response to FDA Information Request: Microbiology	Form FDA 356h and Attachment 1
02-Aug-10	0027	Response to FDA Information Request: Additional Analyses - cSSSI	• Cerexa results for cSSSI additional analysis. • Response to FDA's staphylococcus aureus question on subject 00020646. • Inform FDA of surgical error.
02-Aug-10	0028	Response to FDA Information Request: CMC - Additional Stability Data	• Package Insert changed to exclude "anhydrous acetic acid free" • USAN name
04-Aug-10	0029	Briefing Book	Form FDA 356h, including 10 hard copies and 10 CDs of PDF of Briefing Book.
09-Aug-10	0030	Response to FDA Information Request: CABP Statistical Analyses	Response to FDA email 02Aug10 regarding mismatch FDA observed between Cerexa and FDA data
06-Aug-10	0031	Response to FDA Information Request: Clinical Pharmacology	Form FDA 356h and Attachment 1
10-Aug-10	0032	Response to FDA Information Request: Antipyretic Dataset Request	Flag cSSSI antipyretic and anti-inflammatory medication use and response at Day 3 for the FDA-defined MITT population
18-Aug-10	0033	Response to FDA Information Request: Clinical Pharmacology	Reviewer requested that Cerexa provide all datasets used in simulations (in .csv format), and all the codes for simulation, PKPD target attainment assessment and exposure assessment based on renal function in Reports ICPD 00174-8 and ICPD 00174-9 submitted in NDA 200-327.
19-Aug-10	0034	Response to FDA Information Request: Request for Additional Case Report Forms	FDA requested additional information on seven case report forms (CRFs) for study P903-08: 5426-08064 5426-08160 5428-08006 5428-08007 5428-08010 5428-08075 5428-08098

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20-Aug-10	0035	Response to FDA Briefing Document	Cerexa has a number of significant concerns regarding the proposed in vitro susceptibility test interpretive criteria and requests for a teleconference with the FDA.
24-Aug-10	0036	Briefing Book - addendum	Briefing book addendum - Identify differences in interpretive criteria proposed by the Agency for S. aureus, S. pneumoniae and H. influenzae described in Tables 4.2 and 4.3 on page 10 of the FDA Briefing Book.
30-Aug-10	0037	General Correspondence - Comments to FDA Briefing Materials	Identified some factual errors to FDA breifing book and request an erratum to the briefing package
16-Sep-10	0038	Response to FDA Information Request: Request for Additional Analyses	Response to FDA request dated 25 August 2010 - additional information for our Phase 3 cSSSI studies (P903-06 and P903-07) regarding the key sensitivity analysis on Study days and in additional subgroups. Analyses is provided per Cerexa's proposed logic.
20-Sep-10	0039	Response to FDA Information Request: Request for Additional Analyses	Response to FDA request dated 25 August 2010 - additional information for our Phase 3 cSSSI studies (P903-06 and P903-07) regarding the key sensitivity analysis on Study days and in additional subgroups. Analyses is provided per FDA's logic.
21-Sep-10	0040	Labeling: Draft labeling	Updated draft package insert - includes track changed PI which includes ad hoc information and MRSA in CABP
24-Sep-10	0041	Response to FDA Information Request: Pediatric Timeline	Pediatric timeline/dates for PREA studies
13-Oct-10	0042	Amendment to a Pending Application	New Drug Application: Draft Labeling
13-Oct-10	0043	Amendment to a Pending Application	New Drug Application: Updated Draft Labeling
14-Oct-10	0044	Amendment to a Pending Application	Post market Requirement and Post Market Commitment
18-Oct-10	0045	Amendment to a Pending Application	Post market Requirement and Post Market Commitment
18-Oct-10	0046	Amendment to a Pending Application	Draft Labeling
20-Oct-10	0047	Amendment to a Pending Application	Updated vial Label
27-Oct-10	0048	Amendment to a Pending Application	Draft Labeling
28-Oct-10	0049	Amendment to a Pending Application	Post market Requirement and Post Market Commitment